Official Title of Study:

A Phase 1/2, open-label, single arm, multicohort, multicenter trial to evaluate the safety and efficacy of JCAR017 in pediatric subjects with relapsed/refractory B-ALL and B-NHL (TRANSCEND PEDALL)

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A PHASE 1/2, OPEN-LABEL, SINGLE ARM, MULTICOHORT, MULTICENTER TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF JCAR017 IN PEDIATRIC SUBJECTS WITH RELAPSED/REFRACTORY B-ALL AND B-NHL (TRANSCEND PEDALL)

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TRANSCEND PEDALL

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{See appended electronic signature page}	
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Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

A Phase 1/2, open-label, single arm, multicohort, multicenter trial to evaluate the safety and efficacy of JCAR017 in pediatric subjects with relapsed/refractory B-ALL and B-NHL (TRANSCEND PEDALL).

Indication

CD19+ relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL) and B-cell non-Hodgkin lymphoma (B-NHL) (comprised of diffuse large B-cell lymphoma [DLBCL], Burkitt lymphoma [BL] or primary mediastinal large B-cell lymphoma [PMBCL]) in pediatric subjects.

Objectives

Primary Objective

Phase 1:

- To identify the recommended Phase 2 dose (RP2D) of JCAR017 in pediatric subjects with CD19+ r/r B-ALL.

Phase 2:

To evaluate the following efficacy endpoints of the JCAR017 RP2D identified in Phase 1, in three pediatric disease cohorts:

- Cohort 1 (r/r B-ALL): Overall response rate (ORR) defined as proportion of subjects with complete response (CR) or complete response with incomplete blood count recovery (CRi) on Day 28 that must be confirmed on Day 56
- Cohort 2 (MRD [minimal residual disease] positive [MRD+] B-ALL): MRD negative rate defined as proportion of subjects with a negative MRD response on Day 28 that must be confirmed on Day 56
- Cohort 3 (r/r B-NHL [DLBCL, BL, or PMBCL]): ORR defined as proportion of subjects with a CR or partial response (PR) on Day 28

Study Design

This is a Phase 1/2, open-label, single arm, multicohort study incorporating the mTPI-2 dose escalation design in Phase 1 and a Simon's Optimal two-stage design in Phase 2 to evaluate the safety and efficacy of JCAR017 in pediatric subjects with CD19+ r/r B-ALL and B-NHL.

Phase 1

Up to 5 dose levels of JCAR017 will be evaluated.

Enrollment will commence in pediatric subjects with r/r B-ALL at Dose Level 1 (DL1) of $0.05x10^6$ chimeric antigen receptor (CAR)+ T cells/kg (maximum dose of $5x10^6$ JCAR017 CAR+ T cells [non-weight adjusted]). If this dose is confirmed to be safe and tolerable, additional subjects will be enrolled at higher dose(s) up to $0.75 x10^6$ CAR+ T cells/kg (maximum of $75x10^6$ JCAR017 CAR+ T cells [non-weight adjusted]) with the aim to identify the RP2D. Dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm with a target dose limiting toxicity (DLT) rate of 30% and an equivalence

interval of 25% to 35%. A dose level will be considered unsafe, with no additional pediatric subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% (ie, P (DLT > 30%|data) > 95%) with at least 3 pediatric subjects treated at that dose level. For a dose level to be declared safe per the mTPI-2 algorithm, at least 3 DLT-evaluable pediatric subjects must have completed the DLT period and the level estimated to be safe.

Once the RP2D for JCAR017 has been selected, additional subjects will be enrolled until at least 10 pediatric subjects are treated at the identified RP2D. The final number of pediatric subjects enrolled and treated, will depend on the number of dose levels tested and the number of DLTs observed within each dose level. Dose finding data from subjects who have become MRD+ or MRD negative upon restaging prior to initiation of lymphodepleting therapy will be evaluable for the DLT analysis and inform the identification of the RP2D.

A Safety Review Committee (SRC) will convene regularly during Phase 1 to review DLTs and recommend a Phase 2 dose based on an integrated assessment of the safety, pharmacokinetic (PK) data and preliminary efficacy information from at least 10 pediatric subjects treated at the RP2D. Analysis of the JCAR017 manufactured product may also be considered.

Phase 2

Up to 71 primary endpoint evaluable pediatric subjects (< 18 years of age) will be treated at the RP2D in one of the 3 cohorts listed below. The sample size for Cohorts 1 and 2 is calculated according to Simon's Optimal two-stage design and based on the primary endpoints of ORR (Cohorts 1 and 3) and MRD negative rate (Cohort 2).

The 10 or more pediatric subjects treated at the RP2D in Phase 1 will form part of the sample size (ie, Cohort 1 and Cohort 2). Therefore, the protocol intends to treat 81 primary endpoint evaluable pediatric subjects in Phase 2, if warranted by the evaluation of results at the completion of the first stage of the study in each cohort.

- Cohort 1: 48 r/r B-ALL evaluable pediatric subjects (13 subjects in Stage 1 and 35 subjects in Stage 2)
- Cohort 2: 23 MRD+ B-ALL evaluable pediatric subjects (9 subjects in Stage 1 and 14 subjects in Stage 2)
- Cohort 3: 10 r/r B-NHL (DLBCL, BL, or PMBCL) evaluable pediatric subjects (due to the very low incidence rate and therefore expected low subject accrual, there is no formal sample size for this arm).

Celgene may elect to explore the identified RP2D in up to 20 additional B-ALL subjects between 18 and 25 years of age in an optional cohort in Phase 2, if it is determined that the risk-benefit profile is such that exploration is warranted after consultation with the SRC.

Study Flow for Individual Subjects

The study will have the following sequential periods: Pre-Treatment Period (screening and leukapheresis and JCAR017 product generation), Treatment Period (lymphodepleting [LD] chemotherapy followed by infusion of JCAR017) and Post-Treatment Follow-up Period. Prior to initiation of any study procedure (screening), subjects must provide informed consent/assent. Once enrolled, subjects will undergo an unstimulated leukapheresis to enable JCAR017 cell

product generation. Subjects may receive optional bridging chemotherapy and upon successful JCAR017 cell product generation, will enter the Treatment Period to receive LD chemotherapy followed by infusion of JCAR017.

In Phase 1, subjects will be treated with JCAR017 at a rate of no more than 1 subject per 14 days after the prior subject receiving the JCAR017 infusion, regardless of site. Once the RP2D has been identified, additional subjects enrolled in Phase 1 at the selected RP2D will be treated with JCAR017 at a rate of no more than 1 subject per site, per week.

In Phase 2, subjects will be treated with JCAR017 at a rate of no more than 1 subject per site per week.

In addition, a staggered dosing approach will also be utilized for all new sites without prior experience of administering CAR T cell therapies as follows:

- 1st subject infusion, wait 14 days
- 2nd subject infusion, wait 14 days

Following completion of this site-staggered enrollment approach, the site may proceed with subject enrollment as communicated by Celgene.

Following the Treatment Period, subjects will then enter the Post-Treatment Follow-Up Period for disease progression/relapse, safety, CAR T cell persistence, second primary malignancies and survival follow up for 2 years after administration of JCAR017 unless the subject is lost to follow-up. Post-study follow-up for survival, relapse, long-term toxicity, second primary malignacies and lentiviral vector safety will continue under a separate long-term follow-up (LTFU) protocol for up to 15 years after the JCAR017 infusion as per health authority regulatory guidelines. All subjects who either complete the Post-Treatment Follow-up period or who prematurely withdraw after JCAR017 infusion will enroll into the LTFU study at the end of study (EOS) visit or at the time of withdrawal, respectively.

An independent Data Safety Monitoring Board (DSMB) will monitor the study conduct.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Phase 1: Male or female subjects, < 18 years of age, with CD19+ B-ALL who are r/r after ≥ 1 line of chemotherapy, relapsed after hematopoietic stem cell transplantation (HSCT), or are otherwise ineligible for HSCT.

Phase 2: Male or female subjects, ≤ 25 years of age, with CD19+ B-ALL or B-NHL who are r/r after ≥ 1 line of chemotherapy, relapsed after HSCT, or are otherwise ineligible for HSCT. Three pediatric (< 18 years of age) cohorts of subjects will be enrolled: Cohort 1: r/r B-ALL; Cohort 2: MRD+ B-ALL; Cohort 3: r/r B-NHL (DLBCL, BL, or PMBCL). B-ALL subjects between 18 and 25 years of age may also be enrolled in an optional cohort in Phase 2.

Enrollment and treatment of subjects will be restricted to a weight of ≥ 6 kg.

B-NHL subjects ≥ 18 years of age will not be eligible for this protocol. B-NHL subjects with secondary central nervous system (CNS) involvement are allowed.

Length of Study

This study will enroll over approximately [redacted] months.

The End of Trial is defined as either the date of the last visit of the last subject completing the Post-Treatment Follow-up Period or the date when the last subject enters the LTFU study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

Study Treatments

Following enrollment in the study, an unstimulated leukapheresis collection will be performed on each subject to obtain a sufficient quantity of [redacted] for the production of the JCAR017 investigational product (IP).

If necessary, anticancer treatment (ie, bridging chemotherapy) is allowed for disease control while JCAR017 is being manufactured, after leukapheresis but prior to LD chemotherapy. Subject must continue to have CD19-positive disease, including measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) for B-NHL subjects, and meet eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of LD chemotherapy.

Subjects will receive 3 days of fludarabine intravenously (IV) (30 mg/m^2) and cyclophosphamide IV (300 mg/m^2) for LD chemotherapy. Two to 7 days after completion of LD chemotherapy, JCAR017 will be administered by IV infusion as a single dose on Day 1. The final JCAR017 drug product consists of a single infusion of two individually formulated CD4+CAR+ and CD8+CAR+ T cell suspensions administered in a 1:1 ratio in a formulation containing dimethyl sulfoxide (DMSO).

In Phase 1, up to 5 dose levels of JCAR017 will be evaluated. The first dose level will be $0.05x10^6$ CAR+ T cells/kg (maximum dose of $5x10^6$ JCAR017 CAR+ T cells [non-weight adjusted]). The declared RP2D will be applied in Phase 2. JCAR017 dosing will be capped at 100kg for all dose levels.

Overview of Key Efficacy Assessments

In the r/r setting, clinical activity based on the induction of complete responses is commonly recognized as a valid endpoint for the evaluation of the activity of a therapy. The key efficacy assessments to be measured include peripheral count, bone marrow (BM) count, cerebrospinal spinal fluid (CSF), physical examination, evaluation of CNS symptoms, disease specific imaging (ie, CT or MRI), and B-symptoms (ie, NHL). Minimal residual disease in B-ALL subjects will be assessed by a validated assay in BM samples. A first response assessment will be performed 28 days after JCAR017 infusion.

Efficacy response for B-ALL subjects will be assessed using the 2019 National Comprehensive Cancer Network (NCCN) response criteria guidelines for pediatric ALL.

Efficacy response for B-NHL subjects will be assessed using the 2015 international pediatric NHL response criteria guidelines.

An Independent Review Committee (IRC) will review all the efficacy data for each subject and confirm the response to therapy. The response assessment for the primary endpoint will be based only on the evaluations made by the IRC.

Minimal residual disease response rate, post-infusion transplant status and time-to-event endpoints such as duration of response (DOR), relapse-free survival (RFS), event-free survival (EFS), best overall response (BOR) and overall survival (OS) will be assessed as secondary efficacy endpoints to ascertain that treatment has a clinically meaningful outcome for these subjects at the end-stage of the disease.

Overview of Key Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities (type, frequency, and severity) will be collected. Adverse events of special interest (AESIs) include cytokine release syndrome (CRS), neurotoxicity, prolonged cytopenias, infections, tumor lysis syndrome (TLS), macrophage activation syndrome, infusion reactions, and hypogammaglobulinemia. These events will be carefully monitored during JCAR017 administration and during follow-up. The following safety assessments will also be monitored:

- The timing and length of inpatient hospitalization
- Physical exam and laboratory evaluations to monitor closely for neurologic changes, CRS, and fever
- [redacted] monitoring for [redacted] vector sequences
- Surveillance for second primary malignancies

Subjects will be followed for 2 years after the JCAR017 infusion (unless subject is lost to follow-up or dies) and will then enter into a separate LTFU study.

Safety monitoring boundaries based on the incidence of Grade 3 or above JCAR017-related AESIs are established using a Bayesian framework (ie, Thall and Simon stopping boundary), to help detect safety signals and to assure acceptable risk/benefit ratio during the course of the study. If the safety boundaries are crossed, an ad-hoc DSMB meeting will be held to review the data and provide recommendation about the study continuation, as appropriate.

Statistical Methods

A feasibility endpoint will be conducted on the first 10 pediatric subjects enrolled for whom a manufacturing process was initiated to assess the percentage of product that is manufactured successfully. If product generation is successful for < 70% (< 7/10 subjects), the study will be temporarily suspended and reviewed by Celgene/DSMB.

Assuming a 18% enrollment dropout rate, a total of 124 pediatric subjects may be enrolled to ensure that approximately 101 primary endpoint evaluable subjects are treated with JCAR017.

Up to 20 additional B-ALL subjects between 18 and 25 years of age may also be treated in Phase 2.

Primary Endpoint Analysis:

Phase 1:

The target DLT rate is set as 30%. The mTPI-2 method will be used to guide dose escalation and the RP2D will be estimated using isotonic regression based on the DLT evaluable analysis set. A dose level will be considered unsafe, with no additional pediatric subjects enrolled at that dose

level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% (ie, P (DLT > 30%|data) > 95%) with at least 3 pediatric subjects treated at that dose level. For a dose level to be declared safe per the mTPI-2 algorithm, at least 3 DLT-evaluable pediatric subjects must have completed the DLT period and the level estimated to be safe. The DLT evaluable analysis set includes all pediatric subjects at a given dose level who have received conforming JCAR017 cell product and who have either experienced a DLT or were followed for the full DLT evaluation period.

Phase 2:

The sample size for Cohorts 1 and 2 is calculated according to Simon's Optimal two-stage design and based on the primary endpoints of ORR (Cohorts 1 and 3) and MRD negative rate (Cohort 2). The 10 or more pediatric subjects treated at the RP2D in Phase 1 will form part of the sample size (ie, Cohort 1 and Cohort 2) in Phase 2.

Cohort 1 (r/r B-ALL): With a 1-sided 5% significance level, 80% power and the boundary to reject the null hypothesis of ORR = 75% vs. the boundary to accept the alternative hypothesis of ORR = 90%, a total of 48 evaluable subjects are required; 13 subjects in Stage 1 and 35 subjects in Stage 2. At least 11 subjects with a confirmed response are required in Stage 1 to proceed into Stage 2 and a total of 41 or more subjects (Stage 1 and 2) are required to have a confirmed response to declare the study successful in this cohort (ie, a target ORR of 83%).

Cohort 2 (MRD+ B-ALL): With a 1-sided 5% significance level, 80% power and the boundary to reject the null hypothesis of MRD negative rate = 60% vs. the boundary to accept the alternative hypothesis of MRD negative rate = 85%, a total of 23 evaluable subjects are required; 9 subjects in Stage 1 and 14 subjects in Stage 2. At least 7 subjects with a confirmed MRD negative response are required in Stage 1 to proceed into Stage 2 and a total of 18 or more subjects (Stage 1 and 2) are required to have a confirmed MRD negative response to declare the study successful in this cohort (ie, a target MRD response rate of 75%).

Cohort 3 (r/r B-NHL [DLBCL, BL, or PMBCL]): Due to the very low incidence rate and therefore expected low subject accrual, there is no formal sample size for this arm; instead, this disease indication will act to gain exploratory efficacy data in this population being treated with JCAR017 at the RP2D. For this reason, the sample size has been set at 10 subjects.

Primary endpoint in Phase 2 will be based on the Efficacy Analysis Population, defined as subjects who fulfilled all study eligibility criteria and received a JCAR017 infusion with conforming product. Subjects ineligible for analysis of the primary endpoints will be replaced.

For r/r B-ALL subjects (Cohort 1) with morphologic evidence of leukemia, response rate will be measured by the percentage of subjects achieving a CR or CRi on Day 28, confirmed on Day 56. Subjects without a response assessment on either Day 28 or Day 56 will be considered a non-responder for purposes of the primary endpoint.

For MRD+ patients (Cohort 2), MRD negative rate will be measured by the percentage of subjects achieving MRD negative status on Day 28, confirmed on Day 56. Subjects with an unknown MRD status on either Day 28 or Day 56 will be considered non-responders for purposes of the primary endpoint.

For r/r B-NHL subjects (Cohort 3), response rate will be measured by the percentage of subjects achieving CR or PR on Day 28. Subjects with an unknown response status on either Day 28 or Day 56 will be considered non-responders for the purposes of the primary endpoint.

[redacted]

Safety analysis will be based on the Safety Analysis Population, defined as all subjects receiving JCAR017 infusion. Data shall be analyzed according to system organ class and preferred term, presented in frequency tables and reported by dose level, disease cohort and in aggregate.

Efficacy data will be analyzed by the non-selected dose levels from Phase 1 and disease cohort (Phase 2 subjects and subjects treated at the RP2D in Phase 1).

Efficacy and safety for subjects aged 18 to 25 years shall be fully reported alongside and in aggregate with pediatric subjects aged < 18 years of age. A risk-group sub-analysis with descriptive statistics and comparison between groups will be included as part of the overall analysis.

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1.1. Disease Background

1.1.1. Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is classified by the World Health Organization (WHO) (Vardiman, 2009) as a precursor lymphoid neoplasm of primarily the B-cell type with only about 10% to 15% of cases involving T cells (Tasian, 2015). Precursor B-cell ALL (B-ALL), defined by the expression of CD79a, CD19, human leukocyte antigen – antigen D related (HLA-DR), and other B-cell antigens accounts for 80% to 85% of childhood ALL and about 30% of all childhood cancers. Acute lymphoblastic leukemia is the most prevalent cancer among children and adolescents in the United States (US), representing 20% of all cancers diagnosed in persons aged < 20 years. The overall incidence of pediatric ALL during 2001 to 2004 was 34.0 cases per 1 million persons. Pediatric ALL has increased during 2001 to 2008 and remained stable during 2008 to 2014. During 2001 to 2014, a total of 38,136 new pediatric ALL cases were diagnosed in the US (Siegel, 2017). In Europe, the overall incidence of ALL is 11 per million per year, but importantly, the incidence peaks in childhood between 2 and 5 years of age (53 per million) and again after 50 years of age (Faderl, 2010). The disease is referred to as lymphoblastic lymphoma (LBL) if the infiltration of bone marrow (BM) is below 25%, and if the BM involvement is > 25% it is leukemia. Immunophenotyping (by flow cytometry) allows the differentiation between B and T precursor ALL and reveals the differentiation status of the malignant B-cells (pro-B, common, pre-B, and mature B-cell), which is essential for treatment selection.

An aggressive cancer of the blood and BM, ALL is the most common form of precursor B-cell neoplasm and is characterized by the proliferation and accumulation of malignant, transformed, and immature hematopoietic cells ("blasts") that accumulate in blood and BM (Gokbuget, 2012). Bone marrow analysis, required for diagnosis, reveals the great majority of children presenting with ALL have a massive leukemic infiltration of more than 50% blast cells by light microscopy. Other lymphatic organs, such as lymph nodes and spleen, can also be affected, as well as non-lymphatic organs, notably the central nervous system (CNS). Less than 10% of pediatric patients have symptomatic CNS involvement, although the frequency is higher in patients with mature B-ALL (Faderl, 2010).

Risk factors for developing ALL include age, exposure to chemotherapy or radiation therapy, and genetic disorders, including Down's syndrome. The risk for developing ALL is highest in children younger than 5 years of age; the risk declines slowly until the mid-20s, and begins to rise again after the age of 50. Approximately 75% of patients with B-ALL have recurrent chromosomal translocations or somatic aneuploidy, many of which have prognostic value (Tasian, 2015). Roughly half of patients with childhood ALL have chromosomal translocations, many of which are undetectable by conventional cytogenetic analysis, but readily detected by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR). The most common of these is the t(12;21) translocation, resulting in an ETV6-runt-related transcription factor 1 fusion that occurs in 20% to 25% of childhood National Cancer Institute (NCI) standard-risk B-ALL. Children with this genetic alteration have an excellent prognosis with a > 95% overall survival (OS) rate (Gaynon, 2012).

Multidrug chemotherapy is the standard treatment option for newly diagnosed childhood ALL. First-line induction therapy for most patients, regardless of presenting features, consists of vincristine, dexamethasone (or prednisone), asparaginase, and doxorubicin — the Berlin-Frankfurt-Münster (BFM) regimen. More than 95% of children receiving first-line therapy will achieve a complete response (CR) within the first 4 weeks of treatment, and 5-year OS rates are approaching 90% (Pui, 2015). For patients presenting with CNS disease, intrathecal triple therapy (methotrexate [MTX], cytarabine, and prednisolone) is used during induction therapy together with intravenous (IV) high-dose MTX to reduce the risk of systemic relapse. These days, because of the risk of delayed neurocognitive impairment, radiation therapy is rarely a component of frontline therapy, but it is used in combination with intrathecal MTX in limited situations where there is a particularly high-risk of CNS relapse (Rabin, 2016).

Once a CR has been achieved, standard postinduction treatment options vary depending on risk group assignment, but all patients receive some form of intensification therapy after CR and before beginning maintenance therapy. The most commonly used therapy includes cyclophosphamide, low-dose cytarabine, and a thiopurine. Maintenance therapy typically consists of mercaptopurine, low-dose MTX, and sometimes vincristine/steroid pulses. The exact therapeutic regimen depends on the risk category of the patient. There has been an attempt to limit exposure to anthracyclines and alkylating agents in children with standard-risk ALL because these drugs increase the risk of late toxicity.

The presence of minimal residual disease (MRD) in these patients, however, necessitates the use of these drugs for maintenance therapy. A previous study assessing the prognostic significance of MRD in high risk B-ALL found that increased levels of MRD were associated with worsening outcomes. MRD > 0.1% at the end of induction is found to be a poor prognostic indicator. Additionally, persistence of MRD at 12 weeks was found to be a very poor prognostic factor, with 5-year disease-free survival (DFS) of approximately 40% (Borowitz, 2015). A blinded prospective study was performed to optimize risk assessment of children with a late isolated, combined or an early combined BM relapse of pre-cursor B-ALL. This study found that patients with intermediate risk BM relapse of ALL, low MRD after induction is associated with an excellent long-term prognosis with conventional chemo-/radiotherapy whereas patients with insufficient response have an extremely poor prognosis. The results of this study confirmed that the MRD level after induction is the strongest independent prognostic factor for the long-term outcome of children with intermediate risk BM relapse of ALL (Eckert, 2011).

Multiple clinical studies with chimeric antigen receptor (CAR) T cells have shown high remission rates among children and adults with relapsed B-ALL. For example, a Phase 1 study was conducted at Memorial Sloan Kettering Cancer Center (MSKCC) involving adults with relapsed B-ALL treated with autologous T cells expressing the 19-28z CAR, a CD-19 specific CAR T. A total of 53 subjects received the T cells. After infusion, cytokine release syndrome (CRS) occurred in 26% of subjects and 1 subject died. Complete remission was observed in 83% of subjects. At a median follow-up of 29 months, the median event-free survival (EFS) was 6.1 months and median OS was 12.9 months. Subjects with a low disease burden (< 5% BM blasts) before treatment had enhanced remission duration and survival. Subjects with a high burden of disease (≥ 5% BM blasts or extramedullary disease) had a greater incidence of CRS and neurotoxic events with shorter long-term survival (Park, 2018).

The ELIANA clinical study evaluated the recently approved CAR T cell therapy, CTL019 (Kymriah™), in relapsed/refractory (r/r) pediatric and young adult subjects with B-ALL. The ELIANA study was a single-arm, open-label, multicenter Phase 2 registration study that included 75 subjects aged 3 to 23 years of age who were primary refractory, refractory to chemotherapy after their first relapse, relapsed after second-line therapy, or ineligible for an allogeneic stem cell transplant (SCT). Subjects in the study received a median of 3 prior lines of therapy, had a median marrow blast percentage of 74% at enrollment, and 61% of subjects had a prior SCT. This study showed that of 75 subjects who received Kymriah and had at least 3 months of follow-up, the overall response rate (ORR) was 81% (60% with CR and 21% with complete remission with incomplete blood count recovery [CRi]). Additionally, all subjects with or without complete hematologic recovery were MRD negative. The median duration of follow-up among subjects who received Kymriah was 13.1 months. The rates of EFS and OS were 73% and 90%, respectively, at 6 months and 50% and 76%, respectively, at 12 months. Furthermore, 47% of subjects experienced grade 3 or 4 CRS within 8 weeks after Kymriah infusion. Neurologic events occurred in 30 of 75 subjects (40%) within 8 weeks after infusion. Ten subjects (13%) had grade 3 neurologic events; no grade 4 events or cerebral edema were reported. Nineteen deaths occurred after Kymriah infusion. Within 30 days after infusion, 1 subject died from cerebral hemorrhage in the context of coagulopathy and resolving CRS, and 1 subject died from progressive disease. More than 30 days after infusion, 17 subjects died due to various causes (Maude, 2018).

Until the recent approval of Kymriah in the US, the best therapeutic option capable of achieving disease eradication for children with relapsed ALL almost invariably included an allogeneic SCT, provided a suitable donor was available and the disease was controlled prior to transplant (Bleakley, 2002). For those who relapse early (< 36 months from diagnosis), the 3-year post-relapse survival is 30%, whereas those who relapse late (≥ 36 months from diagnosis) have a 3-year survival of 57.8% (Freyer, 2011).

1.1.2. Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies with differing clinical courses and responses to treatment (Pinkerton, 2012). The WHO Lymphoma Classification scheme is commonly used to define specific subtypes of lymphoma and subdivides them based on cell of origin (B, T or natural killer [NK]) and the differentiation status of the lymphocytes (Vardiman, 2010). Eighty percent to 90% of NHL are of B-cell origin and express CD19 (Pinkerton, 2012). The prognosis of NHL depends on the histologic type (indolent versus aggressive), stage, age, and treatment. The NHL subtypes that occur in adult and pediatric populations show both similarities as well as distinct differences. Childhood NHL typically displays an aggressive clinical course, while adult NHLs show both indolent and aggressive histological forms. Indolent subtypes of NHL that occur in adults include follicular lymphoma (FL), marginal zone lymphoma (MZL), and chronic lymphocytic leukemia (CLL). Aggressive B-cell subtypes include diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) (Chao, 2013).

Many of the NHL types, including FL, CLL, and MCL, that are relatively common in adults occur very rarely, if at all, in children (Gerrard, 2008). Pediatric B-cell non-Hodgkin's lymphoma (B-NHL), comprises of 3 main histological subtypes, all of which are classified as aggressive: Burkitt lymphoma (BL), DLBCL, and primary mediastinal large B-cell lymphoma

(PMBCL), in descending order of overall incidence. The majority of LBL cases (≥ 75%) are T cell lineage with the remainder having a pre-B or mature B-cell immunophenotyped (Cairo, 2016).

The annual incidence per million inhabitants in the US ranges from 5.9 in children younger than 5 years of age to about 10 in children between 5 and 14 years of age, and 15 in adolescents (approximately 150 in adults) (Minard-Colin, 2015). As a group, all forms of NHL combined account for approximately 7% of new childhood and adolescent cancer diagnoses in Europe (Stiller, 2006); 1436 children and 205 adolescents were diagnosed in Europe between 1993 and 1997 (Stiller, 2006). In Europe, the age-adjusted incidence of NHL in children aged 0 to 14 years is 9.2 per million, and is approximately 2.4-fold higher in males (Stiller, 2006); the incidence of NHL and predominant B-cell histologies in Western Europe is comparable to that of the US. Data from the US Surveillance, Epidemiology, and End Results (SEER) Program provides the age-specific incidences of the 3 pediatric B-NHL histologies. The occurrence of NHL in infants is very rare, and the incidence in adults increases steeply with age. Adolescents, specifically the 15- to 19-year age group, have a higher mortality rate compared to children in the 10- to 14-year age group (Burkhardt, 2012). The most prevalent forms of pediatric B-NHL comprise about 60% of all childhood NHL and are detailed below.

Despite significant progress in treatment, approximately 25% to 30% of children will relapse or experience refractory disease with cure rates less than 30% (Jourdain, 2015).

For both aggressive and indolent subtypes, r/r pediatric B-NHL represents a major treatment challenge since there is no standard of care for salvage regimens, with prognosis after relapse remaining relatively poor. Salvage treatment typically consists of high-dose chemotherapy followed by an intensification phase with either autologous or allogenic hematopoietic SCT (HSCT). Given the poor long-term survival in children with r/r B-NHL and the absence of potential curative therapies, novel approaches are needed for these patients with no effective treatment options.

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma accounts for 10% to 20% of B-cell lymphoma in children and occurs more frequently in adolescents (Minard-Colin, 2015). Diffuse large B-cell lymphoma is the most prevalent form of NHL in children and adolescents combined, occurring with greater frequency in adolescents, and comprising up to 37% of all NHL in the 15 to 19 year age range (Hochberg, 2016; Minard-Colin, 2015). With increasing age, the age-specific incidence (per million) of DLBCL grows from 2.9 in childhood, 5.8 in adolescence, 43 in adults 25 to 64 years of age, and peaks at 300 in adults > 65 years of age.

Burkitt lymphoma

In children ≤ 14 years of age, BL is the most common NHL, comprising 30% to 40% of all NHL in North America and Europe (Molyneux, 2012). It generally arises in the abdomen and/or head and neck region and presents as advanced-stage disease involving the BM and/or CNS in approximately 20% to 25% of patients (Minard-Colin, 2015). The incidence of BL remains relatively constant throughout life, in contrast to other NHL subtypes including DLBCL, which typically increase dramatically with age. Burkitt lymphoma has a distinct epidemiological pattern because of its association with Epstein-Barr virus (EBV) and malaria infections that are endemic in sub-Saharan Africa. In this region, the incidence of BL is estimated at 40 to 50 per

million children < 18 years of age and comprises up to 90% of all NHL diagnoses (Molyneux, 2012). The sporadic form, found in low-risk areas such as North America and Europe, has a much lower incidence of 2 to 4 per million children (Sant, 2010). The incidence of the sporadic form peaks at 6 to 8 years of age and is 3.5 times more common in boys than in girls.

Primary mediastinal large B-cell lymphoma

Until recently, PMBCL was considered as a form of DLBCL, comprising 10% or fewer of all cases (Vitolo, 2016). It is now recognized as a distinct entity in the WHO classification because of its distinct immunophenotype, gene expression profile, and clinical presentation compared to other histologies (Dunleavy, 2015). Owing to the rarity of this form of NHL, data on incidence by age are incomplete. A BFM study group identified a total of 30 children with PMBCL out of a large cohort of 1650 pediatric patients with NHL, or 1.8% of all patients diagnosed with NHL, during the period from 1986 to 1999 (Seidemann, 2003). This rate equates to approximately 9 to 16 cases annually in Europe, and is similar to that seen in the US. The incidence of PMBCL peaks in the third or fourth decade of life and is more common in women (Cairo, 2016; Vitolo, 2016).

1.2. Compound Background

1.2.1. CD19 as a Therapeutic Target

CD19 is a 95 kDa glycoprotein present on B-cells from early development until differentiation into plasma cells (Stamenkovic, 1988). It is a member of the immunoglobulin superfamily and functions as a positive regulator of the B-cell receptor by lowering the signaling threshold for B-cell activation (Brentjens, 2011; LeBien, 2008; Stamenkovic, 1988). CD19 is an attractive therapeutic target because it is expressed by most B-cell malignancies, including B-NHL (Davila, 2012). Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from those of the B-cell lineage. Additionally, CD19 is not shed in the circulation, which limits off-target adverse effects (Shank, 2017).

1.2.2. CD19-Targeted Chimeric Antigen Receptors

CD19-specific CARs are generated by the fusion of a single chain variable fragment (scFv), derived from an anti-CD19 monoclonal antibody (mAb), to an intracellular signaling domain. Expression of the CD19-directed CAR in autologous T cells is achieved by ex vivo transduction using a recombinant retroviral or lentiviral vector. The CAR is expressed on the T cell surface and redirects the transfected T cells to CD19-expressing lymphoma cells, leading to CD19-specific tumor cell recognition, lysis, cytokine secretion, and T cell proliferation (Sadelain, 2013). In clinical studies, CD19-targeted CARs have demonstrated encouraging activity in adult and pediatric subjects with r/r B-ALL and B-NHL (Gardner, 2017).

CD19 CAR T cell therapy is an effective adoptive cell treatment and has the potential to overcome chemo-refractory B-cell leukemia and lymphoma (Makita, 2017), as demonstrated in the ELIANA clinical study and recent approval of Kymriah in the US (Maude, 2018).

1.2.3. JCAR017 Investigational Drug Product

The final JCAR017 investigational drug product being evaluated in this study consists of a single infusion of two individually formulated CD4+CAR+ and CD8+ CAR+ frozen T cell suspensions

in media containing dimethyl sulfoxide (DMSO) that are thawed and infused separately. JCAR017 is administered by IV infusion.

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

Refer to the Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational product (IP).

1.2.4. Clinical Experience with JCAR017 and Related CAR T Cell Products

A Phase 1 study of 45 children and young adults with r/r B-ALL was conducted using SCRI-CAR19v1, a similar CD19 CAR T product of defined CD4/CD8 composition, uniform CAR expression, and limited effector differentiation (Study PLAT-02; NCT02028455). The product met all defined specifications in 93% of enrolled subjects. The maximum tolerated dose (MTD) was $1x10^6$ CAR T cells/kilogram (kg), and there were no deaths or instances of cerebral edema attributable to product toxicity. The overall intent-to-treat MRD negative remission rate for this Phase 1 study was 89%. The MRD negative remission rate was 93% in subjects who received a CAR T cell product and 100% in the subset of subjects who received fludarabine and cyclophosphamide lymphodepletion (Gardner, 2017).

JCAR017 is currently being evaluated in adult subjects with relapsed and refractory B-cell NHL (study 017001 - TRANSCEND NHL001; NCT02631044) (Abramson, 2017). A total of 108 patients had received JCAR017 at the time of data cutoff (October 9, 2017). Preliminary data suggest promising antitumor activity of JCAR017 in these heavily pretreated, poor prognosis R/R patients with aggressive NHL (median of 3 prior lines of therapy). In 65 patients with R/R DLBCL the best ORR reported was 80% and the complete response rate (CRR) at 6 months 47%, and an acceptable safety profile. No dose-limiting toxicity (DLT) was observed at Dose Level 2 (DL2) (JCAR017 infusion of 1×10^8 viable CAR+ T cells). Pharmacokinetics analyses showed that in vivo expansion of JCAR017+ T cells peaks around day 11 after infusion of JCAR017. This is consistent with the reported safety with most important toxicities (severe cytokine release syndrome [sCRS], neurotoxicity [NT]) occurring within the first 14 days after infusion.

Out of 91 patients evaluable for safety, major safety findings include CRS, NT, and hematological disorders, including neutropenia, thrombocytopenia, and anemia. The most significant toxicities reported have been sCRS and NT. Cytokine release syndrome was observed in 32 (35%) patients treated, with only 1 patient developing sCRS (Grade 3-4). NT was observed in 19% of the patients, of which 12% developed severe NT (Grade 3-4). Median time to onset of CRS after JCAR017 infusion was 5 days, median time to onset of NT was 10 days. The median time to resolution to grade 1 or better was 5 days for CRS and 10 days for NT. No unexpected early or late toxicities were reported. No cerebral edema, fatal CRS or NT were observed, and symptoms were reversible and manageable with appropriate treatment intervention and close monitoring (Abramson, 2017).

See the JCAR017 IB for further details.

1.3. Rationale

1.3.1. Study Rationale and Purpose

The purpose of this Phase 1/2 study is to evaluate the efficacy and safety of JCAR017 in pediatric subjects with r/r CD19+ B-ALL and B-NHL.

The JCAR017 IP is composed of autologous CD8+ and CD4+ T cells that express a CD19-specific CAR. CD19 is an attractive therapeutic target because it is expressed in most B-cell malignancies. In clinical studies, CD19-targeted CARs have demonstrated encouraging anti-leukemic activity in r/r adult and pediatric patients with B-ALL and other B-cell malignancies, as seen in the ELIANA clinical study and recent approval of Kymriah in the US (Davila, 2012; Li, 1993; Li, 1996; Maude, 2018).

JCAR017 differs from other CAR T products in that it is a defined composition product that consists of CD4+CAR+ and CD8+CAR+ CD19-targeted T cells. It is known that CD4+ T cells enhance CD8+ effector T cell persistence, memory formation, and trafficking to antigen-rich tissues. Activated CD8+ T cells have also shown poor survival when CD4+ T cell help is absent, and CD4+ T cell help is required during recall expansion of memory CD8+ T cells (Bos, 2010; Toes, 1999). Likewise, CD4+CAR+ T cells enhance CD8+CAR+ cytolytic effector T cell function both in vitro and in vivo (Adusumilli, 2014). Thus, since JCAR017 has a defined ratio of CD4+CAR+ to CD8+CAR+ CD19-targeted T cells, persistence, trafficking to the tumor, and antitumor activity may be improved compared with CAR T cell investigational drug products without a defined composition.

Post-Treatment follow-up (for 2 years after JCAR017 infusion) will assess subjects for progressive disease (PD)/relapse, safety, CAR T cell persistence, second primary malignancies and survival, while long-term follow-up (LTFU) (up to 15 years after JCAR017 infusion) will assess subjects for survival, relapse, long-term toxicity, second primary malignancies and lentiviral vector safety. Note: The long-term follow-up may exceed 15 years if the subject does not achieve Tanner Stage 5 by the end of the 15-year safety follow-up period.

1.3.2. Rationale for the Study Design

1.3.2.1. Phase 1

The dose finding part of this study will utilize the mTPI-2 design (Guo, 2017) to determine the recommended Phase 2 dose (RP2D) of JCAR017 in pediatric subjects with CD19+ r/r B-ALL. The mTPI-2 design uses a Bayesian statistical framework and a beta/binomial hierarchic model to compute the posterior probabilities of three intervals that reflect the relative distance between the toxicity rate of each dose level to help identify the RP2D. Once the RP2D of JCAR017 has been selected, additional subjects will be enrolled until at least 10 pediatric subjects are treated at the identified RP2D. The mTPI-2 design will allow to treat a higher percentage of patients at the MTD, as well as reaching the MTD sooner than more conventional dose escalation designs.

The Phase 1 will exclusively enroll subjects (< 18 years of age) with morphologically r/r B-ALL since these are the subjects with the highest unmet medical need and have few, if any, treatment alternatives. Once the RP2D is identified, the Phase 2 (Section 1.3.2.2) will enroll additional

pediatric cohorts, including subjects with a better prognosis and safety profile (eg, MRD+ B-ALL) who are not expected to receive major bridging chemotherapy.

Results from the PLAT-02 study showed no significant difference in CAR T related toxicities in pediatric subjects with morphological versus MRD+ or MRD negative disease (Gardner 2017). Therefore, dose finding data from B-ALL pediatric subjects with morphologic disease as well as those with MRD+ or MRD negative disease upon restaging prior to initiation of lymphodepleting therapy will be evaluable for the DLT analysis and inform the identification of the RP2D in the Phase 1. Consequently, pediatric subjects with r/r B-ALL (mostly necessitating bridging chemotherapy) and MRD+ and MRD negative B-ALL disease (converted following bridging chemotherapy; combined incidence expected to be approximately 30% based on PLAT-02 data) will be treated in Phase 1 (see Figure 1). Safety information on B-ALL pediatric subjects with both morphologic and MRD+ as well as MRD negative disease will emerge from Phase 1 and will be available prior to enrolling pediatric subjects with MRD+ B-ALL disease in Phase 2.

1.3.2.2. Phase 2

Phase 2 will include pediatric subjects (< 18 years of age) treated at the identified RP2D in the 3 cohorts listed below:

Cohort 1 (r/r B-ALL): this cohort serves to demonstrate the efficacy and safety of JCAR017 in pediatric subjects with r/r B-ALL.

Cohort 2 (MRD+ B-ALL): this cohort serves to demonstrate the efficacy and safety of JCAR017 in pediatric subjects with MRD+ B-ALL.

Cohort 3 (r/r B-NHL [DLBCL, BL, or PMBCL]): this cohort serves to demonstrate the efficacy and safety of JCAR017 in pediatric subjects with r/r B-NHL.

Cohort 1 and 2 will incorporate Simon's Optimal two-stage design which accommodates the most appropriate endpoint for these diseases in this patient population, response rate. Cohort 3 will enroll a set number of subjects for the purpose of gaining preliminary efficacy information.

Celgene may elect to explore the identified RP2D in up to 20 additional B-ALL subjects between 18 and 25 years of age in an optional cohort in Phase 2, if it is determined that the risk-benefit profile is such that exploration is warranted after consultation with the SRC.

Recent results from clinical studies have demonstrated promising CR rates, including MRD negative responses, with the use of CAR T cell products directed against CD19 in r/r pediatric ALL (Gardner, 2016). More specifically, early results from an ongoing clinical study of a similar CAR T cell product, SCRI-CAR19v1, in pediatric r/r B-ALL (Study PLAT-02) conducted in the US has demonstrated exceptionally high response rates of 93%; all responders were MRD negative (Gardner, 2017). Overall, the data reveal a reasonably safe, efficacious and durable therapy across indications and suggest that CD19-targeted CAR T cells could become one of the most effective therapeutic agents for treating r/r B-ALL.

To optimize safety, Phase 1 subjects will be treated with JCAR017 at a rate of no more than 1 subject per 14 days after the prior subject receiving the JCAR017 infusion, regardless of site. Once the RP2D has been identified, additional subjects enrolled in Phase 1 at the selected RP2D will be treated with JCAR017 at a rate of no more than 1 subject per site, per week. In Phase 2, subjects will be treated with JCAR017 at a rate of no more than 1 subject per site per week.

In addition, a staggered dosing approach will also be utilized for all new sites without prior experience of administering CAR T cell therapies as follows:

- 1st subject infusion, wait 14 days
- 2nd subject infusion, wait 14 days

Following completion of this site-staggered enrollment approach, the site may proceed with subject enrollment as communicated by Celgene.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

1.3.3.1. Rationale for JCAR017 Dose

SCRI-CAR19v1, a CAR T cell product that is similar to JCAR017 has been well tolerated at doses from 0.5 x 10^6 to 1 x 10^6 CAR+ T cells/kg in pediatric subjects with B-ALL after lymphodepleting (LD) chemotherapy with fludarabine and cyclophosphamide in a Phase 1 study (PLAT-02) of 45 children and young adults. The maximum tolerated (and total) dose of this Phase 1 study was 1 x 10^6 CAR T cells/kg. Overall, 33% of subjects developed reversible severe cytokine release syndrome (sCRS) and/or reversible severe neurotoxicity (sNT), toxicities that are frequently associated with CAR T cell therapies. There were no deaths or instance of cerebral edema attributable to product toxicity (Gardner, 2017). While the PLAT-02 trial demonstrated encouraging clinical activity with an overall manageable toxicity profile in pediatric B-ALL, it should be noted that process changes are needed to standardize product consistency and process robustness are necessary to support the conduct of the trial at multiple clinical sites with a global manufacturing process.

An adverse event (Grade 4 neurotoxicity) observed in the first pediatric subject with B-ALL dosed in JCAR017-BCM-004 prompted Celgene to re-evaluate the dosing strategy. Analysis of the JCAR017 manufactured product characteristics showed very active cells as a result of the necessary process manufacturing modifications, suggesting a lower safe starting dose should be identified. Trials using a defined composition product autologous CD8+CAR+ and CD4+CAR+ T cells that express a CD19-specific CAR such as JCAR014 (Turtle, 2016b) and SCRI-CAR19v1 (Gardner, 2017) suggests that a 10-fold dose reduction significantly reduced toxicity while preserving efficacy and maintaining a positive risk/benefit.

Based on these considerations, an initial Phase 1 dose finding with a 10-fold dose reduction to a starting dose (Dose Level 1 [DL1]) of 0.05×10^6 CAR T cells/kg will be pursued. If this dose is confirmed to be safe and tolerable, additional subjects will be enrolled at higher dose(s) up to 0.75 x10^6 CAR+ T cells/kg utilizing an mTPI-2 algorithm with the aim to identify the Recommend Phase 2 Dose (RP2D). The concern that DL1 may be non-efficacious in B-ALL pediatric subjects with morphologic disease will be addressed with one-time retreatment with intra-patient dose-escalation for subjects with no Day 28 response and who have shown no severe toxicity at DL1. After Day 28 response assessment, these subjects will receive repeat lymphodepletion followed by a single dose of JCAR017 at 0.10×10^6 CAR T cells/kg (total of 0.15x10^6 CAR T cells/kg and equaling DL2).

Additional changes that are designed to support safe administration of JCAR017 in the pediatric B-ALL setting include increased frequency of cytokine and PK determinations (to allow comprehensive subject data assessment during dose escalation) and modification of the toxicity

management algorithm incorporating the learnings from diagnosis and management of the first subject dosed in the study.

JCAR017 dosing will also be capped at 100 kg at all dose levels to avoid potential overdosing.

Subjects 18 to 25 years of age will receive JCAR017 at the RP2D to be studied.

1.3.3.2. Rationale for Lymphodepleting Chemotherapy Dose

Lymphodepleting chemotherapy has been shown to be critical to the subsequent anti-CD19 efficacy of CAR T cells.

Pre-clinical studies of CAR-modified T cells targeting B-cell malignancies suggest that optimal anti-CD19 T cell cytotoxic function and subsequent persistence is enhanced by LD chemotherapy prior to adoptive T cell transfer (James, 2009; Kochenderfer, 2010; Pegram, 2012).

The Phase 1 PLAT-02 study found that all subjects who received prescribed LD chemotherapy with fludarabine and cyclophosphamide achieved uniform engraftment of functional CAR T cells in blood and subsequent development of B-cell aplasia (BCA) and MRD negative remission, irrespective of cell dose (Gardner, 2017). The results from the clinical studies complement pre-clinical data demonstrating that LD chemotherapy is critical to the subsequent anti-CD19 efficacy of CAR T cells.

JCAR017, given as a single flat dose after LD chemotherapy, has been evaluated in the Study PLAT-02 and in the Study 017001 (TRANSCEND NHL 001). The TRANSCEND study has shown that dose levels 1 and 2 (5×10^7 CAR+ T cells, and 1×10^8 CAR+ T cells, respectively) given as a single flat dose after lymphodepletion are safe and have shown preliminary efficacy. The lymphodepletion regimen used was cyclophosphamide (300 mg/m^2/day x 3 days) combined with fludarabine (30 mg/m^2/day x 3 days) (flu/cy) (Abramson, 2017).

Based on this data, the LD chemotherapy regimen employed in the current protocol is the same as that used in the TRANSCEND study. Subjects will receive fludarabine IV 30 mg/m^2 and cyclophosphamide IV 300 mg/m^2 for 3 days. This regimen was selected to limit toxicity and retain anticancer activity, as well as to optimize cellular expansion and anticancer activity after treatment with JCAR017.

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objectives
The primary objective of Phase 1 is to identify the recommended Phase 2 dose (RP2D) in pediatric subjects with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL). The primary objective of Phase 2 is to evaluate the efficacy of JCAR017 at the RP2D, in the following pediatric disease cohorts: • Cohort 1 (r/r B-ALL): Overall response rate (ORR) defined as proportion of subjects with a complete response (CR) or complete response with incomplete blood count recovery (CRi) on Day 28 that must be confirmed on Day 56 • Cohort 2 (minimal residual disease [MRD]+ B-ALL): MRD negative rate defined as proportion of subjects with an MRD negative response on Day 28 that must be confirmed on Day 56 • Cohort 3 (r/r B-cell non-Hodgkin lymphoma [B-NHL] (diffuse large B-cell lymphoma [DLBCL], Burkitt lymphoma [BL] or primary mediastinal large B-cell lymphoma [PMBCL]): ORR defined as proportion of subjects with a CR or partial response (PR) on Day 28
Secondary Objectives
The secondary objectives for Phase 1 and Phase 2 are: • Evaluate the feasibility of manufacturing JCAR017 measured by the percentage of product generated successfully (Phase 1 only) • Evaluate ORR in the non-selected dose levels from Phase 1 • Evaluate safety and tolerability assessments during 24 months after JCAR017 infusion • To further evaluate efficacy by assessing the duration of response (DOR), relapse-free survival (RFS), event-free survival (EFS), best overall response (BOR) and overall survival (OS) during 24 months after JCAR017 infusion • Evaluate the percentage of r/r B-ALL subjects who achieve CR or CRi with no MRD detected in bone marrow (BM) (below the level of detection [<0.01%] by a validated assay) assessed during 24 months after JCAR017 infusion • Assess the percentage of subjects who achieve a response after JCAR017 infusion and then proceed to hematopoietic stem cell transplant (HSCT) • Characterize the pharmacokinetic (PK) profile of JCAR017 assessed during 24 months after JCAR017 infusion

Table 1: Study Objectives (Continued)

Exploratory Objectives
The exploratory objectives apply to both Phase 1 and Phase 2 and are to: • Analyze the best response and ORR by sub-group/risk-group, including cytogenetics/genetic sub-group(s) • Analyze impact of prior HSCT on response by comparing ORR in subjects with to those without prior HSCT [redacted] • Describe the effect of treatments directed at severe cytokine release syndrome (sCRS) and neurotoxicity on duration and severity of these events [redacted] • Measure Patient Reported Outcomes • Measure hospital resource utilization

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Phase 1 Primary	Recommended Phase 2 dose (RP2D) in relapsed/refractory (r/r) pediatric B-cell acute lymphoblastic leukemia (B-ALL)	Integral assessment of safety, pharmacokinetic (PK), preliminary efficacy and number of subjects experiencing a dose-limiting toxicity (DLT)	28 days after JCAR017 infusion
Phase 2 Primary	Cohort 1 (r/r B-ALL): Overall response rate (ORR)	Percentage of subjects achieving a confirmed complete response (CR) or complete response with incomplete blood count recovery (CRi)	On Day 28 and must be confirmed on Day 56
	Cohort 2 (MRD+ B-ALL): Minimal residual disease (MRD) negative rate	Percentage of subjects achieving a confirmed CR or CRi with an MRD negative bone marrow (<0.01% tumor cells by a validated assay)	On Day 28 and must be confirmed on Day 56

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Cohort 3 (r/r B-cell non-Hodgkin lymphoma [B-NHL]): ORR	Percentage of subjects achieving CR or partial response (PR)	Day 28
Secondary	Safety	Type, frequency, and severity of adverse events (AEs), including serious adverse events (SAEs) and laboratory abnormalities	2 years after JCAR017 infusion
	Feasibility of manufacturing JCAR017 (Phase 1 only)	Percentage of JCAR017 product generated successfully	During pretreatment period (leukapheresis to JCAR017 generation)
	Overall response rate (ORR) in the non-selected dose levels from Phase 1	Percentage of r/r B-ALL subjects achieving a best overall response (BOR) of confirmed CR or CRi	On Day 28 and must be confirmed on Day 56
	Duration of response (DOR)	Time from first response until progressive disease (PD), disease relapse, or death from any cause, whichever occurs first	2 years after JCAR017 infusion
	Relapse-free survival (RFS)	Time from JCAR017 infusion to documentation of PD, disease relapse, or death due to any cause, whichever occurs first	2 years after JCAR017 infusion
	Event-free survival (EFS)	Time from JCAR017 infusion to PD, disease relapse, start of a new anticancer therapy, or death from any cause, whichever occurs first	2 years after JCAR017 infusion
	Overall survival (OS)	Time from JCAR017 infusion to time of death due to any cause	2 years after JCAR017 infusion

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	MRD negative response rate (non-selected dose levels in Phase 1 and Cohort 1 in Phase 2 only)	Percentage of B-ALL subjects achieving confirmed CR or CRi with an MRD negative BM (< 0.01% tumor cells by a validated assay)	2 years after JCAR017 infusion
	Best Overall Response (BOR)	Percentage of r/r B-NHL subjects achieving BOR of CR or PR	2 years after JCAR017 infusion
	Rate of hematopoietic stem cell transplant (HSCT) after response to JCAR017 infusion	Percentage of subjects who achieve a response after JCAR017 infusion and then proceed to HSCT	2 years after JCAR017 infusion
	Pharmacokinetics (PK) by ddPCR	Maximum concentration (Cmax), time to peak concentration (Tmax), area under the curve (AUC) including maximum expansion and duration of persistence of JCAR017	2 years after JCAR017 infusion
Exploratory	Response assessment by sub-group/risk-group	Sub-group/risk-group analysis of best response and overall response rate	2 years after JCAR017 infusion
	Overall response rate with and without prior HSCT	Sub-group analysis of overall response rate with and without prior HSCT	2 years after JCAR017 infusion
	[redacted]		

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	[redacted]		
	Resolution of severe cytokine release syndrome (sCRS) and/or neurotoxicity	Response and time to resolution for sCRS and/or neurotoxicity to interventions	90 days after JCAR017 infusion
	Patient Reported Outcomes	Patient Reported Outcomes measured by Pediatric Quality of Life Inventory (PedsQL) Core module, Cancer module, Multidimensional Fatigue Scale, and Family Impact Module	2 years after JCAR017 infusion
	Hospital resource utilization	Number of inpatient intensive care unit (ICU) days, and outpatient visits	2 years after JCAR017 infusion

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 1/2, open-label, single arm, multicohort study incorporating Simon's Optimal two-stage design to evaluate the safety and efficacy of JCAR017 in pediatric subjects with CD19+ r/r B-ALL and B-NHL (Figure 1).

3.1.1. Phase 1

Up to 5 dose levels of JCAR017 will be evaluated as described in Section 7.2.5.

Enrollment will commence in pediatric subjects (< 18 years of age) with r/r B-ALL at DL1 of $0.05x10^6$ CAR+ T cells/kg (maximum dose of $5x10^6$ JCAR017 CAR+ T cells [non-weight adjusted]). If this dose is confirmed to be safe and tolerable additional pediatric subjects will be enrolled at higher dose(s) up to 0.75 x106 CAR+ T cells/kg (maximum of $75x10^6$ JCAR017 CAR+ T cells [non-weight adjusted]) with the aim to identify the pediatric RP2D. Dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm (Guo, 2017) with a target DLT rate of 30% and an equivalence interval of 25% to 35% (Appendix G). A dose level will be considered unsafe, with no additional pediatric subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% (ie, P (DLT > 30%|data) > 95%) with at least 3 pediatric subjects treated at that dose level. For a dose level to be declared safe per the mTPI-2 algorithm, at least 3 DLT-evaluable pediatric subjects must have completed the DLT period and the level estimated to be safe. Enrollment to the next dose level will be prioritized over the same dose level, if the next dose level cohort is open for enrollment. The decision to open a dose level for enrollment will be made by Celgene, informed by the Safety Review Committee (SRC), considering results from the mTPI-2 algorithm and preliminary efficacy. For the first 5 pediatric subjects treated at a dose level, no more than 3 pediatric subjects can be in the DLT period simultaneously at a dose level that has not yet been shown to be safe per the mTPI-2 algorithm. Up to 3 additional pediatric subjects are allowed to be within the DLT period at lower dose levels that have already been shown to be safe.

Once the RP2D for JCAR017 has been selected, additional subjects will be enrolled until at least 10 pediatric subjects are treated at the identified RP2D. Dose finding data from subjects who have become MRD+ or MRD negative upon restaging prior to initiation of lymphodepleting therapy will be evaluable for the DLT analysis and inform the identification of the RP2D in Phase 1 (Figure 1).

During Phase 1, the SRC whose members include the medical monitor(s), drug safety physician, statistician, and a subset of investigators will recommend the RP2D based on an integrated assessment of the safety, pharmacokinetic (PK) and preliminary efficacy information from at least 10 pediatric subjects treated at the RP2D. Analysis of the JCAR017 manufactured product may also be considered in the RP2D determination. The SRC may recommend overriding the mTPI-2 algorithm's allocation of a subject or subjects to a particular dose level that is estimated to be safe per the mTPI-2 algorithm.

3.1.2. Phase 2:

Up to 71 primary endpoint evaluable pediatric subjects (< 18 years of age) will be treated in one of the 3 cohorts listed below.

The sample size for Cohorts 1 and 2 is calculated according to Simon's Optimal two-stage design and based on the primary endpoints of ORR (Cohorts 1 and 3) and MRD negative rate (Cohort 2). The 10 or more pediatric subjects treated at the RP2D in Phase 1 will form part of the sample size (ie, Cohort 1 and Cohort 2). Therefore, the protocol intends to treat 81 primary endpoint evaluable pediatric subjects in Phase 2, if warranted by the evaluation of results at the completion of the first stage of the study in each cohort.

- Cohort 1: 48 r/r B-ALL evaluable pediatric subjects (13 subjects in Stage 1 and 35 subjects in Stage 2)
- Cohort 2: 23 MRD+ B-ALL evaluable pediatric subjects (9 subjects in Stage 1 and 14 subjects in Stage 2).
- Cohort 3: 10 r/r B-NHL (DLBCL, BL, or PMBCL) evaluable pediatric subjects (due to the very low incidence rate and therefore expected low subject accrual, there is no formal sample size for this arm).
  - Note: B-NHL subjects with secondary CNS lymphoma involvement are eligible; however, subject selection must consider clinical risk factors for severe neurological AEs and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject.

Pediatric B-ALL subject enrollment will start with Cohort 1 (morphologic disease only). Pediatric subjects with MRD+ B-ALL disease at screening will only be able to be enrolled into Cohort 2 after enrollment into Cohort 1 is completed. However, Cohort 1 subjects who convert from morphologic disease to MRD+ B-ALL disease following bridging chemotherapy (and prior to LD chemotherapy) will be enrolled into Cohort 2 at any time during Phase 2

Celgene may elect to explore the identified RP2D in up to 20 additional B-ALL subjects between 18 and 25 years of age in an optional cohort in Phase 2, if it is determined that the risk-benefit profile is such that exploration is warranted after consultation with the SRC.

3.1.3. Study Flow for Individual Subjects

The study will have the following sequential periods: Pre-Treatment Period (screening and leukapheresis), Treatment Period and Post-Treatment Follow-up Period (Figure 2). Prior to initiation of any study procedures (screening), subjects must provide informed consent/assent. Once enrolled, subjects will undergo an unstimulated leukapheresis to enable JCAR017 cell product generation. Subjects may receive optional bridging chemotherapy and upon successful JCAR017 cell product generation, will enter the Treatment period and receive LD chemotherapy followed by infusion of JCAR017. All subjects completing the Pre-treatment Period will be re-assessed to ensure that inclusion/exclusion criteria are still met prior to receiving LD chemotherapy and JCAR017 infusion.

- Pre-treatment Period:

  - Screening, leukapheresis and JCAR017 product generation. Subjects may receive a single cycle of commercially available anticancer treatment (ie, bridging chemotherapy) and/or supportive care at the Investigator's discretion while the JCAR017 cell product is being manufactured.

- Treatment and Post-Treatment Follow-up Period:
  - Treatment Period (LD chemotherapy to Day 56): administration of LD chemotherapy followed by a single infusion JCAR017 consisting of two individually formulated CD4+CAR+ and CD8+CAR+ T cell at a starting dose of $0.05x10^6$ CAR+ T cells/kg (2 to 7 days after completion of LD chemotherapy). Lymphodepleting chemotherapy will consist of fludarabine/cyclophosphamide.
  - Post-treatment Follow-up Period (after Day 56 to end of study [EOS]): subjects will be followed for progressive disease (PD)/relapse, safety, CAR T cell persistence, second primary malignancies and survival for 2 years after administration of JCAR017 unless subject is lost to follow-up.

In Phase 1, subjects will be treated with JCAR017 at a rate of no more than 1 subject per 14 days after the prior subject receiving the JCAR017 infusion, regardless of site. Once the RP2D has been identified, additional subjects enrolled in Phase 1 at the selected RP2D will be treated with JCAR017 at a rate of no more than 1 subject per site, per week.

In Phase 2, subjects will be treated with JCAR017 at a rate of no more than 1 subject per site per week.

In addition, a staggered dosing approach will also be utilized for all new sites without prior experience of administering CAR T cell therapies as follows:

- 1^{st} subject infusion, wait 14 days
- 2^{nd} subject infusion, wait 14 days

Following completion of this site-staggered enrollment approach, the site may proceed with subject enrollment as communicated by Celgene.

The first response assessment will be performed 28 days after JCAR017 infusion.

One interim analysis is planned for Cohort 1 and Cohort 2, each, and will be based on cleaned efficacy data relating to the primary endpoint. In Cohort 1, the interim analysis will be conducted once the first 13 subjects eligible for the primary endpoint have all had their efficacy data relating to the primary endpoint become available. In Cohort 2, the interim analysis will be conducted once the first 9 subjects eligible for the primary endpoint have all had their efficacy data relating to the primary endpoint become available.

If at least 11 subjects in Cohort 1 achieve a confirmed response during Stage 1, then Cohort 1 will proceed to Stage 2; otherwise Cohort 1 shall close to further enrollment. Similarly, if at least 7 subjects in Cohort 2 achieve a confirmed MRD negative response during Stage 1, then Cohort 2 will proceed to Stage 2; otherwise Cohort 2 shall close to further enrollment.

During the final analysis, if at least 41 of the 48 subjects in Cohort 1 achieve a confirmed response across Stages 1 and 2, it will be concluded that JCAR017 treatment is successful in the pediatric r/r B-ALL population. Similarly, during the final analysis, if at least 18 of the 23

subjects in Cohort 2 achieve a confirmed MRD negative response across Stages 1 and 2, it will be concluded that JCAR017 treatment is successful in the pediatric MRD+ B-ALL population.

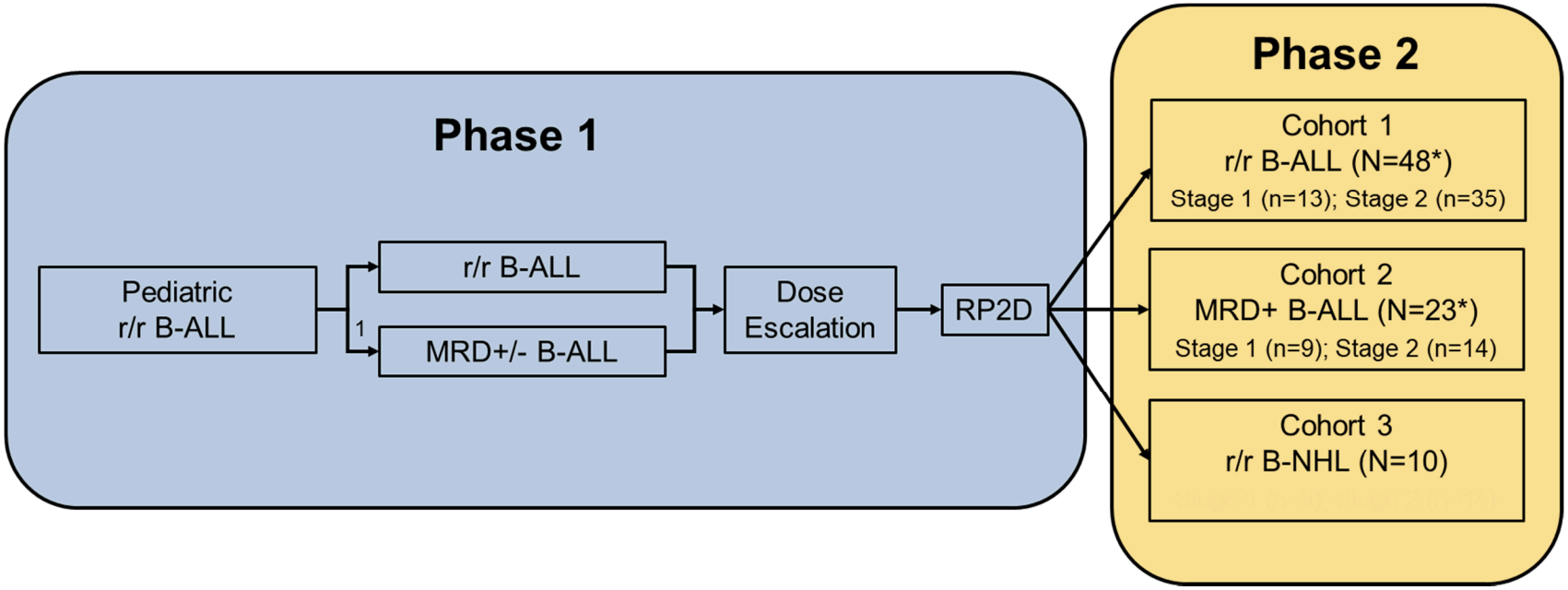
Post-study follow-up for survival, relapse, long-term toxicity, second primary malignancies and lentiviral vector safety will continue under a separate LTFU protocol for up to 15 years after JCAR017 infusion as per health authority regulatory guidelines. In addition, details on subsequent antineoplastic treatments will be documented for at least 5 years. Note: The long-term follow-up may exceed 15 years if the subject does not achieve Tanner Stage 5 by the end of the 15-year safety follow-up period.

All subjects who either complete the Post-Treatment Follow-up period or who prematurely withdraw from the study after JCAR017 infusion will enroll into LTFU at the end of study visit or at the time of withdrawal, respectively. Subjects discontinuing the treatment period before JCAR017 infusion will complete the EOS visit and then discontinue from the study.

An independent data safety monitoring board (DSMB) (Section 9.9.3) with multidisciplinary representation will evaluate activity of the study treatment and safety data periodically to monitor benefit-to-risk of this protocol. The function of the DSMB is to monitor the safety and activity of the study treatment and to provide recommendations about the study continuation, as appropriate. Details of the DSMB structure, composition, and roles/responsibilities will be outlined within a DSMB charter.

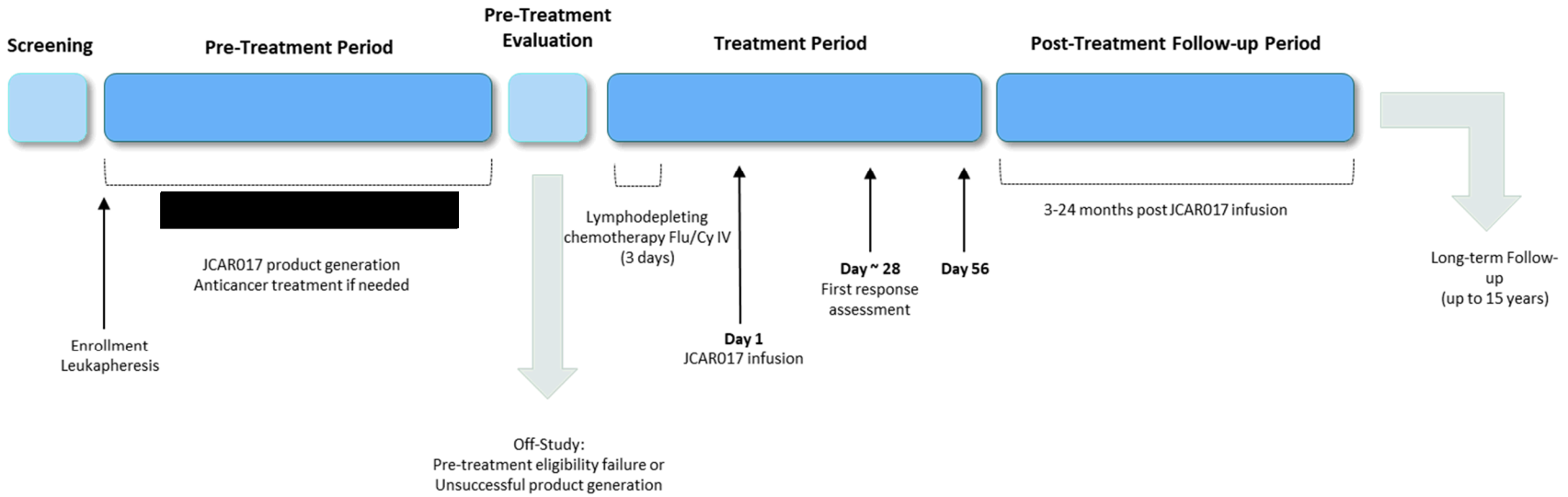
The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 1: Overall Study Design



Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; MRD = minimal residual disease; NHL = non-Hodgkin lymphoma; RP2D = recommended Phase 2 dose; r/r = relapsed/refractory.
* Includes subjects from Phase 1 treated at the RP2D.
[1] Optional bridging chemotherapy may convert r/r B-ALL into MRD+ and MRD negative B-ALL disease.

Figure 2: Study Schematic



Abbreviations: Cy = cyclophosphamide; Flu = fludarabine; IV = intravenous.

3.2. Stopping Rules

Adverse events and serious adverse events (SAEs) are expected to occur frequently in this study based on the subject 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 JCAR017 will be the primary criteria for pausing or stopping the study. Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the Data Safety Monitoring Board (DSMB), Celgene and the Medical Monitor. Decisions to pause enrollment or terminate the study will be communicated promptly to Investigators, to the Institutional Review Boards (IRBs)/Ethics Committees (Ecs), Institutional Biosafety Committees (IBCs) (if applicable), and to the appropriate regulatory authorities.

3.2.1. 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 28 days after JCAR017 infusion:

- Life-threatening (Grade 4) toxicity attributable to protocol therapy (JCAR017 infusion +/- LD chemotherapy) that is unexpected, unmanageable (ie, does not resolve to Grade 3 or lower within 7 days), and unrelated to anticancer treatments between leukapheresis and LD chemotherapy
- Death related to JCAR017 infusion

Expected toxicities are described in the Reference Safety Information (RSI) in the IB. These toxicities include but are not limited to: Grade 4 CRS, neurotoxicity (eg, encephalopathy and/or seizures), and hypotension. The expected toxicities may also result in secondary toxicities of Grade 4 renal toxicity, hepatic toxicity, or other organ involvement. Consistent with the Reference Safety Information in the JCAR017 Investigator Brochure all life-threatening or fatal events will be considered unexpected for the purpose of reporting suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities, and if considered related to JCAR017 treatment will be reported in an expedited fashion.

The study may be terminated for the following reasons:

- Any subject develops uncontrolled JCAR017 proliferation that is unresponsive to treatment
- Any subject develops detectable replication-competent lentivirus (RCL) during the study
- Celgene, IRB/EC, SRC, or DSMB decides that subject safety may be compromised by continuing the study
- Celgene decides to discontinue/limit the development of JCAR017 in the indications under evaluation.

3.3. Safety Monitoring Boundaries

Safety monitoring boundaries based on Bayesian framework (Thall, 1994) have been established to help detect signals that may occur during the course of the study. The boundaries are non-binding and based on the cumulative number of subjects who have received at least one dose of JCAR017 and who experienced at least one of the following toxicity events within 30 days of a JCAR017 infusion:

- A Grade 3 or above, JCAR017-related, treatment-emergent neurological toxicity
- A Grade 4 treatment-emergent AESI that is unmanageable or fails to resolve to Grade 3 or lower after 7 days

Whenever the safety boundaries are crossed, an ad-hoc DSMB meeting will be held to review the data and provide recommendation about the study continuation, as appropriate. The DSMB may override the safety stopping boundaries to recommend study continuation based on clinical and overall risk benefit considerations. Additional information will be detailed in the JCAR017-BCM-004 Statistical Analysis Plan (SAP).

3.4. Study Duration for Subjects

This study will enroll over approximately [redacted] months and will consist of 3 periods:

- The Pretreatment Period will consist of screening for eligibility, leukapheresis, JCAR017 product generation and a pretreatment evaluation (prior to LD chemotherapy).
- The Treatment Period will start with LD chemotherapy, followed by JCAR017 infusion 2 to 7 days after completion of LD chemotherapy and follow-visits through Day 56. The first response evaluation will be performed at approximately 28 days after JCAR017 infusion.
- The Post-Treatment Follow-up Period will consist of further efficacy and safety follow-up visits at approximately 3, 6, 9, 12, 18 and 24 months after JCAR017 infusion.

The duration of participation for subjects who complete the study will be approximately 26 months. All subjects who receive JCAR017 will be asked to enroll into the LTFU protocol after completion of this study (Section 6.8).

3.5. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject completing the Post-Treatment Follow-up period or the date when the last subject enters the LTFU study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

This study will enroll and treat approximately up to 101 total pediatric subjects (up to 30 in Phase 1 and up to 71 additional subjects in Phase 2) should all dose levels and cohorts enroll the maximum number of subjects and assuming no subjects are replaced.

Up to 20 additional subjects between 18 and 25 years of age may also be enrolled in Phase 2.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Phase 1: Subject < 18 years of age and weighs ≥ 6 kg at the time of signing the informed consent form (ICF)/informed assent form (IAF).

   Phase 2: Subject ≤ 25 years of age and weighs ≥ 6 kg at the time of signing the ICF/IAF.
2. Subject (when applicable, parental/legal representative) must understand and voluntarily provide permission to the ICF/IAF prior to conducting any study-related assessments/procedures.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Investigator considers the subject is appropriate for adoptive T cell therapy.
5. Evidence of CD19 expression via flow cytometry (peripheral blood or bone marrow) or immunohistochemistry (bone marrow biopsy)
6. Subject has a Karnofsky score of ≥ 50 (subjects ≥ 16 years of age) or a Lansky score ≥ 50 (subjects < 16 years of age).
7. Diagnosis of B-cell ALL or B-cell NHL as defined below:

   Phase 1: Subjects with r/r B-ALL, defined as morphological evidence of disease in BM (5% or greater lymphoblast by morphology) and either of the following:

   - First or greater marrow relapse, or
   - Any marrow relapse after allogeneic HSCT, or
   - Primary refractory defined as not achieving a CR or a CRi after 2 or more separate induction regimens (or chemo-refractory as not achieving CR/CRi after 1 cycle of standard chemotherapy for relapsed leukemia), or
   - Ineligible for allogeneic HSCT

   Note: Subjects will be included regardless of MRD status.

   Phase 2: Subjects with one of the following:

   - Cohort 1: r/r B-ALL, defined as morphological evidence of disease in BM (5% or greater lymphoblast by morphology) and either:
     - First or greater marrow relapse, or

  - Any marrow relapse after allogeneic HSCT, or
  - Primary refractory defined as not achieving a CR or a CRi after 2 or more separate induction regimens (or chemo-refractory as not achieving CR/CRi after 1 cycle of standard chemotherapy for relapsed leukemia), or
  - Ineligible for allogeneic HSCT.
- Cohort 2: MRD+ B-ALL, defined as:
  - < 5% lymphoblasts by morphology with,
  - MRD detected by a validated assay at a frequency of 1×10^{-4} or greater in BM cells. Subjects eligible for enrollment in Cohort 2 are those with MRD positive morphologic CR2 after re-induction when these subjects had previously experienced an early relapse (< 36 months) after first-line chemotherapy. Subjects who are in MRD+ morphologic CR3 and later, regardless of time to relapse in earlier lines, are also eligible.

    Subjects who are in morphologic relapse at screening (r/r B-ALL) and become MRD+ after bridging chemotherapy are also eligible for treatment in Cohort 2.
- Cohort 3: r/r B-NHL (DLBCL, BL or PMBCL), defined as
  - Measurable disease after 1 or more lines of chemotherapy and/or having failed HSCT or being ineligible for HSCT.

    Note: B-NHL subjects with secondary CNS lymphoma involvement are eligible however subject selection must consider clinical risk factors for severe neurological AEs and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject.

8. Subjects with Philadelphia chromosome positive ALL are eligible if they are intolerant to or have failed one or more lines of tyrosine-kinase inhibitor (TKI) therapy or if TKI therapy is contraindicated.
9. Adequate organ function, defined as:
   - Adequate BM function to receive LD chemotherapy as assessed by the Investigator.
   - Subject with adequate renal function, which is defined as:
     - Serum creatinine based on age/gender as described below. Subjects that do not meet the criteria but who have a creatinine clearance or radioisotope glomerular filtration rate (GFR) > 70 mL/min/1.73 m^2 are eligible.

Creatinine Clearance Estimation Using the Schwartz Formula

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1.0	1.0
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating glomerular filtration rate (GFR) (Schwartz, 1976) utilizing child length and stature data published by the Center for Disease Control (CDC).

- Alanine aminotransferase (ALT) ≤ 5 x upper limit of normal (ULN) and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or leukemic/lymphomatous infiltration of the liver).
- Adequate pulmonary function, defined as ≤ Grade 1 dyspnea according to Common Toxicity Criteria for Adverse Events (CTCAE) and oxygen saturation (SaO_2) ≥ 92% on room air.
- Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) within 4 weeks prior to leukapheresis.

10. Adequate vascular access for leukapheresis procedure.
11. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals for at least 1 year following LD chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with JCAR017. Therefore, subjects treated with JCAR017 should not donate blood, organs, tissues and cells for transplantation.
12. Female children of childbearing potential (FCCBP) and females of childbearing potential (FCBP) must:
    - Have two negative pregnancy tests as verified by the Investigator (one negative serum beta human chorionic gonadotropin [ß-hCG] pregnancy test result at screening and one negative serum pregnancy test within 7 days prior to the first dose of LD chemotherapy). This applies even if the subject practices true abstinence* from heterosexual contact.
    - Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective and 1 additional effective (barrier) method of

contraception from screening until at least 12 months following LD chemotherapy or JCAR017 infusion, whichever occurs last.

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

Highly effective methods of contraception:

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

Additional effective methods of contraception:

- Male condom
- Diaphragm
- Cervical cap

- Agree to abstain from breastfeeding during study participation and for at least 1 year following LD chemotherapy.
- There are insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with JCAR017. Any decision regarding contraception and breastfeeding after JCAR017 infusion should be discussed with the treating physician.

NOTE: Female Children of Childbearing Potential (FCCBP) is defined as females who have achieved menarche and/or breast development in Tanner Stage 2 or greater and have not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries). Note: Amenorrhea following cancer therapy does not rule out childbearing potential. Female of Childbearing Potential (FCBP) is defined as a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy, has not been naturally postmenopausal (amenorrhea following cancer does not rule out childbearing potential) for at least 12 consecutive months without an alternative medical cause.

13. Male subjects must:

- Practice true abstinence* (which must be reviewed on a monthly basis and source documented) or agree to use a condom during sexual contact with a pregnant female or a FCBP while participating in the study and until at least 12 months following LD chemotherapy even if he has undergone a successful vasectomy.
- There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.

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

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Subject with a history of another primary malignancy that has not been in remission for at least 2 years prior to enrollment.
5. Subjects who have received previous CD19-targeted therapy must have CD19-positive disease confirmed since completing the prior CD19-targeted therapy.
6. Prior CAR T cell or other genetically-modified T cell therapy.
7. Subject with a previous history of or active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection.
8. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection (including tuberculosis) despite appropriate antibiotics or other treatment at the time of leukapheresis or JCAR017 infusion.
9. Subject has presence of acute or chronic graft-versus-host disease (GVHD).
10. Subject with active autoimmune disease requiring immunosuppressive therapy.
11. Subject has cardiac disorders (CTCAE version 4.03 Grade 3 or 4) within the past 6 months.
12. Subject with a concomitant genetic syndrome, with the exception of Down's syndrome.
13. Subject with active CNS disease and significant neurological deterioration. Subjects with CNS-2 or CNS-3 involvement are eligible provided they are asymptomatic and do not have significant neurological deterioration and, in the opinion of the study Investigator, the CNS disease burden can be controlled until JCAR017 infusion.
14. Subject with a history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, cerebral edema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
15. Subject is pregnant or nursing.
16. Subject has used the following:
    - Therapeutic doses of corticosteroids (defined as > 0.4 mg/kg [maximum 20 mg/day prednisone] or equivalent) within 7 days prior to leukapheresis or 72 hours prior to JCAR017 infusion. Physiologic replacement, topical and inhaled steroids are permitted.

- Low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide ≤ 300 mg/m^2) given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to LD chemotherapy.
- Cytotoxic chemotherapeutic agents that are not considered lymphotoxic within 1 week prior to leukapheresis. Oral anticancer agents are allowed if at least 3 half-lives have elapsed prior to leukapheresis.
- Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine) within 2 weeks prior to leukapheresis.
- Experimental agents within 4 weeks prior to leukapheresis unless no response or PD is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis.
- Immunosuppressive therapies within 4 weeks prior to leukapheresis and JCAR017 infusion (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-tumor necrosis factor [TNF], anti-IL-6, or anti-IL-6R).
- Donor lymphocyte infusions (DLI) within 6 weeks prior to JCAR017 infusion.
- Radiation within 6 weeks prior to leukapheresis. Subjects must have PD in irradiated lesions or have additional non-irradiated lesions to be eligible. Radiation to a single lesion, if additional non-irradiated, measurable lesions are present, is allowed up to 2 weeks prior to leukapheresis.
- Allogeneic HSCT within 90 days prior to leukapheresis.

17. Tumor invasion of venous or arterial vessels (B-NHL subjects only).
18. Deep Venous Thrombosis (DVT) or Pulmonary Embolism (PE) within 3 months prior to leukapheresis. Subjects with DVT or PE that occurred longer than 3 months prior to leukapheresis, who still require ongoing therapeutic levels of anti-coagulation therapy, are also excluded.
19. Existence of CD19-negative clone(s) of leukemia cells.

5. TABLE OF EVENTS

Table 3: Table of Events

		Pre-treatment Period			Treatment Period											Post-Treatment Follow-up Period					
	Ref. Section	Screening[cc]	Leukapheresis	Pre-Treatment Evaluation	LD Chemotherapy	JCAR-017 Infusion															
Study Month	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	18	24
Study Day		Up to 14 days before leukapheresis	[redacted]	Within 7 days before LD chemotherapy	Start 5 to 10 days before Day 1[bb]	1[bb]	2	3	4	7	10	14	21	28	56	90	180	270	365	545	730 (EOS) or ET
Visit Window (Days)	-	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±4	±14	±14	±14	±14	±30	±30	±30
STUDY PROCEDURES FOR BOTH B-ALL AND B-NHL SUBJECTS																					
Informed consent/assent	6.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eligibility criteria	4.2	x	x[a]	x[a]	x[a]	x[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	7.3	x	x	x	x	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x
Medical history	6.1	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Performance score	6.9.7	x	x	x	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x
Height	6.9.4	x	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.9.4	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.9.1	x[c]	-	x[c]	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tanner staging	6.9.2	x	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x
Routine neurologic examination	6.9.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 3: Table of Events (Continued)

		Pre-treatment Period			Treatment Period											Post-Treatment Follow-up Period					
	Ref. Section	Screen-ing[cc]	Leuka-pheresis	Pre-Treat-ment Evalua-tion	LD Chemo-therapy	JCAR-017 Infu-sion															
Study Month	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	18	24
Study Day		Up to 14 days before leuka-pheresis	[redacted]	Within 7 days before LD chemo-therapy	Start 5 to 10 days before Day 1[bb]	1[bb]	2	3	4	7	10	14	21	28	56	90	180	270	365	545	730 (EOS) or ET
Visit Window (Days)	-	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±4	±14	±14	±14	±14	±30	±30	±30
Vital signs[d]	6.9.3	x	x[e]	x	x[dd]	x[f]	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
12-lead ECG	6.9.9	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA scan/ECHO	6.9.8	x[g]	-	x[o]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	Table 9	x	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy (FCCBP/FCBP)	Table 9	x	-	x[i]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HLA typing and donor chimerism[j]	6.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	Table 9	x	x	x	x[dd]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coagulation	Table 9	-	-	x	-	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
Chemistry	Table 9	x	x	x	x[dd]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Creatinine clearance	4.2	x	-	-	x[k]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Peripheral CD3+ count	6.1.2	-	x[l]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukapheresis	6.1.2	-	x[m]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LD chemotherapy	6.2.1.2	-	-	-	x[dd]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 infusion	6.2.1.3	-	-	-	-	x[n]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

		Pre-treatment Period			Treatment Period											Post-Treatment Follow-up Period					
	Ref. Section	**Screen-ing[cc]**	**Leuka-pheresis**	**Pre-Treat-ment Evalua-tion**	**LD Chemo-therapy**	**JCAR-017 Infu-sion**															
Study Month	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	18	24
Study Day		**Up to 14 days before leuka-pheresis**	[redacted]	**Within 7 days before LD chemo-therapy**	**Start 5 to 10 days before Day 1[bb]**	**1[bb]**	**2**	**3**	**4**	**7**	**10**	**14**	**21**	**28**	**56**	**90**	**180**	**270**	**365**	**545**	**730 (EOS) or ET**
Visit Window (Days)	-	-	-	-	-	-	-	-	**+1**	**±1**	**±1**	**±2**	**±2**	**±4**	**±14**	**±14**	**±14**	**±14**	**±30**	**±30**	**±30**
Inflammatory markers	Table 9	-	-	x	-	x	x	x	x	x	x	x	x	x[o]	x[o]	-	-	-	-	-	-
Immunoglobulins[p]	Table 9	-	-	x	-	-	-	-	-	-	-	x	x	x	x	x[q]	x[q]	x[q]	x[q]	x[q]	x[q]
CSF assessment	Table 9	x[r]	-	x[r]	-	-	-	-	-	-	-	-	-	x[r]	x[r]	x[r]	x[r]	x[r]	x[r]	x[r]	x[r]
Patient Reported Outcomes (PROs)[ee]	6.13	x	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x
Parent/Caregiver Reported Outcomes[ff]	6.13	x	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x
Hospital resource utilization	6.14	-	-	-	Ongoing																
Disease therapy since study treatment discontinuation	6.2.2	-	-	-	Ongoing																
Adverse events and concomitant medications[p]	8.0 10.0	AEs related to protocol-mandated procedures and associated concomitant medications			All AEs and associated concomitant medications											AEs related to protocol-mandated procedures or JCAR017 and associated concomitant medications					
Survival status	6.7	-	-	-	Ongoing																

Table 3: Table of Events (Continued)

		Pre-treatment Period			Treatment Period											Post-Treatment Follow-up Period					
	Ref. Section	Screen-ing[cc]	Leuka-pheresis	Pre-Treat-ment Evalua-tion	LD Chemo-therapy	JCAR-017 Infu-sion															
Study Month	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	18	24
Study Day		Up to 14 days before leuka-pheresis	[redacted]	Within 7 days before LD chemo-therapy	Start 5 to 10 days before Day 1[bb]	1[bb]	2	3	4	7	10	14	21	28	56	90	180	270	365	545	730 (EOS) or ET
Visit Window (Days)	-	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±4	±14	±14	±14	±14	±30	±30	±30
STUDY PROCEDURES FOR B-ALL SUBJECTS ONLY																					
BMA/BMB	6.10.1	x	-	x[s]	-	-	-	-	-	-	-	-	-	x	x	x	At PD/relapse/as clinically indicated[v]				
Peripheral blood smear	6.10.1	x	-	x[s]	-	-	-	-	-	-	-	-	-	x	x	x	At PD/relapse/as clinically indicated[v]				
MRD evaluation	6.10.1	x	-	x[s]	-	-	-	-	-	-	-	-	-	x	x	x	At PD/relapse/as clinically indicated[v]				
Efficacy assessment (local and IRC)	6.10.1	-	-	-	-	-	-	-	-	-	-	-	-	x[t]	x[t]	x[t]	At PD/relapse/as clinically indicated[v]				

Table 3: Table of Events (Continued)

		Pre-treatment Period			Treatment Period											Post-Treatment Follow-up Period					
	Ref. Section	Screen-ing[cc]	Leuka-pheresis	Pre-Treat-ment Evalua-tion	LD Chemo-therapy	JCAR-017 Infu-sion															
Study Month	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	18	24
Study Day		Up to 14 days before leuka-pheresis	[redacted]	Within 7 days before LD chemo-therapy	Start 5 to 10 days before Day 1[bb]	1[bb]	2	3	4	7	10	14	21	28	56	90	180	270	365	545	730 (EOS) or ET
Visit Window (Days)	-	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±4	±14	±14	±14	±14	±30	±30	±30
STUDY PROCEDURES FOR B-NHL SUBJECTS ONLY																					
BMA/BMB	6.10.2	x[w]	-	-	-	-	-	-	-	-	-	-	-	x[w]	At PD/relapse/as clinically indicated[v,w]						
CT/MRI	6.10.2	x[u]	-	x[u]	-	-	-	-	-	-	-	-	-	x	-	x	x	x	x[v]		
Tumor biopsy[x]	6.10.2	x	-	-	-	-	-	-	-	-	-	-	-	x	At PD/relapse/as clinically indicated[v]						
Efficacy assessment (local and IRC)	6.10.2	-	-	-	-	-	-	-	-	-	-	-	-	x	-	x	x	x	x[v]		
RESEARCH SAMPLES FOR BOTH B-ALL AND B-NHL SUBJECTS																					
Peripheral blood for JCAR017 PK [redacted]	6.11.1	x	-	-	x	x	x	-	x	x	x	x	x	x	x	x	x	x	x	x[y]	x[y]
[redacted]																					

Table 3: Table of Events (Continued)

		Pre-treatment Period			Treatment Period											Post-Treatment Follow-up Period					
	Ref. Section	Screen-ing[cc]	Leuka-pheresis	Pre-Treat-ment Evalua-tion	LD Chemo-therapy	JCAR-017 Infu-sion															
Study Month	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	18	24
Study Day		Up to 14 days before leuka-pheresis	[redacted]	Within 7 days before LD chemo-therapy	Start 5 to 10 days before Day 1[bb]	1[bb]	2	3	4	7	10	14	21	28	56	90	180	270	365	545	730 (EOS) or ET
Visit Window (Days)	-	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±4	±14	±14	±14	±14	±30	±30	±30
[redacted]																					

Abbreviations: AE = adverse event; B-ALL = B-cell acute lymphoblastic leukemia; B-NHL = B-cell non-Hodgkin lymphoma; BM = bone marrow; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CNS = central nervous system; eCRF = electronic case report form; CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; EOS = end of study; ET = early termination; FCBP = female of child-bearing potential; FCCBP = female children of child-bearing potential; FEV_1 = forced expiratory volume in one second; GVHD = graft-versus-host disease; HLA = human leukocyte antigen; IRC = Independent Review Committee; IRT = interactive response technology; IV = intravenous; LD = lymphodepleting; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition scan; [redacted] PD = progressive disease; PK = pharmacokinetic; PRO = patient reported outcome; [redacted] SCT = stem cell transplantation.

[a] Eligibility criteria: Subjects must be evaluated for evidence of active infections prior to the leukapheresis being started. In case of suspected infection, subject should be treated and leukapheresis postponed until the active infection has resolved. The subject must continue to meet pre-treatment eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of LD chemotherapy and JCAR017. In addition, subjects who receive CD19-targeted therapy as anticancer treatment for disease control while JCAR017 is being manufactured, must have CD19-positive disease re-confirmed prior to receiving LD chemotherapy.

[b] If MRD status is unknown at the time of infusion (Day 1), IRT will be retrospectively updated with the MRD status from the central analytical laboratory.

[c] Including GVHD assessment (if applicable).

[d] 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 eCRF.

[e] Vital signs should be taken before and after leukapheresis.

[f] Measured within 15 minutes prior to the first JCAR017 administration, within 15 minutes after IV administration, and approximately every 15 minutes thereafter for the first hour, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the IV administration, vital signs should be monitored as clinically indicated until stable.

[g] Does not need to be done at screening if one performed within 4 weeks prior to leukapheresis.

[h] Infectious disease marker blood sample sent with leukapheresis product and applicable to European sites only. Refer to the MNC collection laboratory manual for further details on where sample is sent for analysis.

[i] Within 48 hours prior to starting LD chemotherapy. Female Children of Childbearing Potential is defined as females who have achieved menarche and/or breast development in Tanner stage 2 or greater and have not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries). Note: Amenorrhea following cancer therapy does not rule out childbearing potential. Female of Childbearing Potential is defined as a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy, has not been naturally postmenopausal (amenorrhea following cancer does not rule out childbearing potential) for at least 12 consecutive months without an alternative medical cause.

[j] Required within 3 months prior to enrollment. Data from local testing will be collected for those subjects with prior allogeneic SCT.

[k] First day of LD chemotherapy only.

[l] Performed within 48 hours prior to leukapheresis to calculate the target whole blood processed volume for the leukapheresis procedure. Refer to the MNC collection laboratory manual for further details.

[m] Should be scheduled as soon as possible after meeting eligibility criteria.

[n] Administered 2 to 7 days after completion of LD chemotherapy. Prior to dose, it must be confirmed that the subject meets criteria for JCAR017 infusion (refer to Section 6.2.1.3).

[o] If clinically indicated.

[p] Please refer to Section 10.1 for details on reporting AEs.

[q] Not required for subjects with documented B-cell recovery without recent use of intravenous immunoglobulin (IVIG).

[r] Required at screening for subjects with suspected or confirmed CNS involvement. CSF assessment is required to be performed if CNS involvement is suspected at the pre-treatment evaluation or at any time during the study as clinically indicated. CNS imaging should be performed as clinically indicated. CSF assessments are not required for subjects in CR/CRi after JCAR017 infusion unless suspicion of CNS relapse.

[s] For B-ALL subjects, the BM assessment (BMA [BMB only if clinically indicated]) performed at the pre-treatment evaluation will serve as the baseline assessment. Subjects will be retrospectively reassigned to the appropriate cohort should their pre-LD chemotherapy disease status show a change from screening. Subjects who demonstrate morphological remission and who are MRD negative upon restaging prior to initiation of lymphodepleting therapy will still be treated and followed on study.

[t] First disease assessment will be performed at 28 days after JCAR017 infusion. If the subject cannot be assessed for CR/CRi due to hypoplastic marrow, a repeat marrow examination should be performed when there is evidence of hematopoietic recovery so that remission can be assessed for the first time. In order for overall response to be categorized as CR or CRi, it must be confirmed at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi.

[u] If the subject has previous imaging within 14 days of screening that is after the last relapse/progression and no anticancer treatment was given between the imaging and screening, those scans can be used as the baseline assessment and do not need to be repeated at screening. In addition, B-NHL subjects who receive anticancer treatment for disease control while JCAR017 is being manufactured will have CT/MRI (chest, neck, abdomen, pelvis) after completion of the intervening anticancer treatment and as close as possible to the start of LD chemotherapy (must be within 7 days prior to start) to confirm measurable disease. B-NHL subjects who do not receive anticancer treatment control while JCAR017 is being manufactured will have CT/MRI scans repeated (must be within 7 days prior to start of LD chemotherapy), only if no scans were done at screening or within 3 weeks prior to the start of LD chemotherapy, to evaluate the tumor load.

[v] To be performed as clinically indicated and at PD/relapse.

[w] For B-NHL subjects, BM assessment (BMA [BMB if clinically indicated]) will be performed at screening. If there is BM involvement at screening, then another BM assessment should be performed at Day 28 and then as clinically indicated after that and at PD/relapse.

[x] To be performed for subjects with accessible disease. Collection of tissue from latest archived tumor biopsy (block or slides) for tumor evaluation at screening. If archival sample is before most recent relapse, a new tumor biopsy is mandated to confirm diagnosis.

[y] [redacted]

[bb] All evaluations, research sampling and laboratory assessments must be done prior to administration of lymphodepleting chemotherapy or JCAR017.

[cc] Screening procedures as standard of care within 30 days prior to signing the ICF/IAF may be used to evaluate study eligibility based on discussion with Celgene Medical Monitor.
[dd] To be done on each day of lymphodepleting chemotherapy. Prior to first dose, it must be confirmed that the subject meets criteria for lymphodepleting chemotherapy as described in Section 6.2.1.1.
[ee] PedsQL Generic Core module, PedsQL Cancer module, and PedsQL multidimensional Fatigue Scale.
[ff] Parent Report PedsQL Generic Core module, Parent Report PedsQL Cancer module, Parent Report PedsQL multidimensional Fatigue Scale, and Parent Report PedsQL Family Impact Module.

6. PROCEDURES

Any questions regarding the protocol should be directed to the Medical Monitor(s) or designee.

6.1. Pre-treatment Period

6.1.1. Screening

Screening may begin once the subject signs the IRB/EC-approved ICF/IAF. Where applicable, institutional decision boards (eg, multidisciplinary tumor boards, Réunion de concertation pluridisciplinaire [RCP]) should be involved for subject selection. If a subject has had a screening procedure as standard of care within 30 days prior to signing the ICF/IAF, it may be used to evaluate study eligibility based on discussion with Celgene. The following assessments must be performed within 14 days prior to enrollment (unless otherwise specified):

- Obtain signed informed consent/assent
- Assess eligibility per inclusion/exclusion criteria. All inclusion/exclusion criteria must be met in order for subjects to enroll in the study.
- IRT registration
- Obtain medical history, including: Disease diagnosis and history, HSCT history, chemotherapy, radiation and surgical history. May include history of toxicities related to prior treatments and allergies.
- Physical examination, including routine 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).
- Tanner staging
- Karnofsky or Lansky performance status assessment
- Cardiac ECHO or MUGA (does not need to be done at screening if one performed within 4 weeks prior to leukapheresis) for LVEF
- 12-lead electrocardiogram (ECG)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Viral serology
  - Serum ß-HCG pregnancy test on FCCBP/FCBP
  - Determination of creatinine clearance
- Local laboratory assessments
  - Human leukocyte antigen (HLA) typing and donor chimerism for subjects who had previous allogeneic HSCT (required within 3 months prior to enrollment)

- Administration of Pediatric Quality of Life Inventory (PedsQL) questionnaires (subject and parent/caregiver as applicable)
- Record all AEs related to protocol-mandated procedures and associated concomitant medications
- Research peripheral blood samples [redacted]:
  - [redacted]
  - JCAR017 PK [redacted]
  - [redacted]
  - [redacted]
- Cerebrospinal fluid assessment is required for subjects with suspected or confirmed CNS involvement. CNS imaging should be performed as clinically indicated.
- B-ALL subjects ONLY:
  - Bone marrow morphological assessment (BM aspirate [BM biopsy only if clinically indicated]).
  - Peripheral blood morphological assessment (PB smear)
  - Minimal residual disease analysis.

  Minimal residual disease will be assessed by a validated assay in BM samples at a central analytical laboratory. Note: Additional BM aspirate may be collected unscheduled if required for additional MRD testing.
- B-NHL subjects ONLY:
  - Bone marrow morphological assessment (BM aspirate [BM biopsy only if clinically indicated])
  - Computer tomography (CT)/magnetic resonance imaging (MRI) (chest, neck, abdomen, pelvis): If the subject has previous imaging within 14 days of screening that is after the last relapse/progression and no anticancer treatment was given between the imaging and screening, these scans can be used as the baseline assessment and do not need to be repeated at screening.
  - Collection of tissue from latest archived tumor biopsy (block or slides) for tumor evaluation. If archival sample is before most recent relapse, a new tumor biopsy is mandated to confirm diagnosis.

6.1.2. Leukapheresis [redacted]

Leukapheresis should be scheduled in coordination with Celgene as soon as possible after the subject has completed screening and has determined to be eligible and is enrolled in the study. Venous access is required for leukapheresis and should be determined according to institutional practice. Should a technical issue arise during the procedure or in the immediate processing of the product such that it cannot be used for JCAR017 production, a second collection procedure

may be performed. Subjects must continue to meet eligibility requirements for repeat leukapheresis.

An unstimulated leukapheresis collection will be performed on each subject to obtain a sufficient quantity of [redacted] for the production of the JCAR017 investigational product. Please refer to the MNC collection manual for further details.

The following assessments will be conducted prior to leukapheresis:

- Eligibility check: subjects must be evaluated for evidence of active infections prior to the leukapheresis being started. In case of suspected infection, leukapheresis should be postponed until the active infection has been treated and has resolved.
- IRT registration
- Medical history
- Karnofsky (subjects 16 ≥ years of age) or Lansky (subjects < 16 years of age) performance status assessment
- Weight
- Vital signs (performed before and after leukapheresis)
- Viral serology testing – infectious disease markers
- Peripheral blood CD3+ count (within 48 hours prior to leukapheresis)
- Hematology (CBC with differential within 24 hours prior to leukapheresis and must include absolute lymphocyte count [ALC].)
- Chemistry
- Record all AEs related to protocol-mandated procedures and associated concomitant medications

Table 4: Washout Periods Prior to Leukapheresis

Treatment	Washout
Systemic Therapy	
Alemtuzumab	6 months
Fludarabine	3 months
Cladribine	3 months
Mitoxantrone	6 weeks
Idarubicin	6 weeks

Table 4: Washout Periods Prior to Leukapheresis (Continued)

Treatment	Washout
Clofarabine	3 months
Arabinoside-C	3 months
Experimental agents (applies only to treatments not listed in Table 4)	4 weeks/3 half-lives (whichever is greater)
Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide >300 mg/m^2, ifosfamide, bendamustine)	2 weeks (with the exception of pegylated asparaginase which is 4 weeks)
Therapeutic doses of corticosteroids (defined as > 0.4 mg/kg [maximum 20 mg/day] prednisone or equivalent)	7 days
Cytotoxic chemotherapeutic agents not considered lymphotoxic (eg, doxorubicin, vincristine, gemcitabine, oxaliplatin, carboplatin, etoposide, etc)	7 days
Intrathecal	
Dexamethasone, methotrexate	7 days
Radiation Therapy	
Radiation, multiple lesions	6 weeks
Radiation, single lesion, if additional non-irradiated measurable lesions are present	2 weeks

6.1.3. Anticancer Treatments Between Leukapheresis and Lymphodepleting Chemotherapy

If necessary, anticancer treatment (ie, bridging chemotherapy) is allowed for disease control while JCAR017 is being manufactured (ie, after leukapheresis and prior to LD chemotherapy). Chemotherapy is allowed if completed at least 7 days prior to the start of LD chemotherapy. If other agents are used, the washout periods noted in the exclusion criteria (see Section 4.3) must be met. The use of therapeutic agents with little/no evidence in the scientific literature for B-ALL or B-NHL should be discussed with Celgene. For B-NHL subjects, local radiation is allowed to a single lesion or subset of lesions. If anticancer treatment is necessary during this time, the pre-treatment CT/MRI assessments, BM assessment, peripheral blood smear, and other pre-treatment study procedures (see Section 6.1.4) must be performed after the anticancer treatment has been completed. Subjects must continue to have confirmed disease, including measurable disease by CT/MRI for B-NHL subjects, and must meet pre-treatment eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of LD chemotherapy.

Note: Subjects who receive CD19-targeted therapy as anticancer treatment for disease control while JCAR017 is being manufactured, must have CD19-positive disease re-confirmed prior to starting LD chemotherapy. Subjects without confirmed CD19+ disease will not be evaluable for the primary endpoint analysis however they will still be able to be treated at Investigator discretion.

6.1.4. Pre-Treatment Evaluation (Within 7 days Prior to Lymphodepleting Chemotherapy)

The following assessments will be conducted:

- **B-ALL subjects ONLY**: (regardless if anticancer treatment for disease control was given while JCAR017 is being manufactured):
  - Bone marrow morphological assessment (BM aspirate [BM biopsy only if clinically indicated])
  - Peripheral blood morphological assessment (PB smear)
  - Minimal residual disease analysis

  Minimal residual disease will be assessed by a validated assay in BM samples at a central analytical laboratory.

  NOTE: The BM assessment performed at the pre-treatment evaluation will serve as the baseline disease assessment. Subjects will be retrospectively reassigned to the appropriate cohort should their pre-LD chemotherapy disease status show a change from screening.

  Subjects who demonstrate morphologic remission and are MRD negative upon restaging prior to initiation of lymphodepleting therapy will continue to be treated and followed on study but will not be considered evaluable for MRD response endpoint and may be replaced.

- **B-NHL subjects ONLY**:
  - For subjects who receive anticancer treatment for disease control while JCAR017 is being manufactured:

    Restaging CT/MRI (chest, neck, abdomen, pelvis) must be performed after completion of the intervening anticancer treatment and as close as possible to the start of LD chemotherapy (must be within 7 days prior to start) to confirm measurable disease.
  - For subjects who did not receive anticancer treatment control while JCAR017 is being manufactured:

    If no scans were done at the study site for screening and within 3 weeks prior to the start of LD chemotherapy, CT/MRI scans must be performed (within 7 days prior to start of LD chemotherapy).

The following assessments will be conducted in all subjects within 7 days prior to starting LD chemotherapy and regardless if any anticancer treatment was received for disease control:

- Confirm subject meets study pre-treatment eligibility criteria
- IRT registration
- Medical history
- Physical examination, including routine neurologic examination, weight, vital signs and GVHD assessment (if applicable).

- Tanner staging
- Karnofsky (subjects ≥ 16 years of age) or Lansky (subjects < 16 years of age) performance status assessment
- 12-lead ECG
- Cardiac ECHO or MUGA for LVEF (if clinically indicated)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
  - Immunoglobulins
  - Serum ß-HCG pregnancy test on FCCBP/FCBP (within 7 days prior to starting LD chemotherapy)
- Cerebrospinal fluid assessment is required to be performed if CNS involvement is suspected or has been confirmed at a previous assessment. CNS imaging should be performed as clinically indicated.
- Administration of Pediatric Quality of Life Inventory (PedsQL) questionnaires (subject and parent/caregiver as applicable)
- Record all AEs related to protocol-mandated procedures (see Table 8) and associated concomitant medications (see Table 7)

6.2. Treatment and Post-treatment Follow-up Periods

6.2.1. Treatment Period

6.2.1.1. Criteria for Treatment

Subject eligibility criteria must be confirmed immediately prior to starting the first cycle of lymphodepleting chemotherapy. Chemotherapy or chemoimmunotherapy given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to lymphodepleting chemotherapy, respecting washout periods in Table 4 and the exclusion criteria (see Section 4.3).

Subjects must also be clinically stable and must have recovered from prior organ (non-hematologic) toxicities to Grade ≤ 2 to receive lymphodepleting chemotherapy and proceed to JCAR017 infusion. Neither lymphodepleting chemotherapy nor JCAR017 treatment will be administered if there is a worsening of performance status, rapid clinical deterioration, or evidence of rapidly progressive disease.

In the absence of infection, isolated AST and/or ALT elevation that can be linked temporally to administration of medication (eg, fungal prophylaxis or bridging chemotherapy) may not preclude treatment of subjects (LD chemotherapy and infusion of JCAR017) after discussion with Celgene's Medical Monitor.

6.2.1.2. Lymphodepleting Chemotherapy (Start 5 to 10 Days Prior to JCAR017 Infusion)

Upon notification from Celgene that JCAR017 will be available, LD chemotherapy should be initiated so as to finish 2 to 7 days prior to JCAR017 infusion. Please see Section 7.2.1 for the recommended administration. Subjects **must** be evaluated for evidence of ongoing infections prior to the LD chemotherapy. In case of suspicion of infection, subject should be treated accordingly, and LD chemotherapy postponed until infection resolution. Delay of lymphodepleting chemotherapy of more than 14 days requires discussion with Celgene and may require rescreening.

The following assessments will be performed prior to dosing on each day of LD chemotherapy administration, unless otherwise noted:

- IRT registration
- Height (only first day of LD chemotherapy) and weight
- Vital signs
- Karnofsky (subjects ≥ 16 years of age) or Lansky (subjects < 16 years of age) performance status assessment
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Serum creatinine or determination of creatinine clearance (required only on first day of LD chemotherapy).

    Lymphodepleting chemotherapy should be withheld if serum creatinine is beyond the maximum value (see Section 4.2) using the Schwartz formula or radioisotope GFR is ≤ 70 mL/min/1.73 m^2.
  - Chemistry
  - Hematology
- Research peripheral blood samples [redacted]
  - For JCAR017 PK [redacted] (only first day of LD chemotherapy prior to dosing)
- Record all AEs and associated concomitant medications
- Hospital resource utilization

6.2.1.3. JCAR017 Administration – Day 1

Based on the risks of adverse events requiring immediate medical intervention, following JCAR017 infusion and prior to discharge from the hospital subjects must meet the following criteria:

- Have dedicated full-time (24-hour care) caregiver support for the first 30 days after JCAR017 infusion

- Stay within a 30-minute transportation ride to the treating clinical trial site for first 30 days after JCAR017 infusion for close monitoring of fever and other signs of CRS or neurotoxicity
- Cannot have disease characteristics that, in the Investigator's clinical judgment, puts the subject at higher risk of complications (eg, tumor lysis syndrome, CRS, neurotoxicity)
- Cannot have a psychosocial condition that puts them at risk for not following instructions

After Day 30, subjects can travel further from site only if they are afebrile for 24 hours and signs and symptoms of CRS and neurotoxicity have completely resolved. If discharged prior to Day 30, self-monitoring of fever is required every 6 to 8 hours (while awake) until 30 days following JCAR017 infusion. Hospitalization is required if there are any signs of fever (≥ 38ºC/100.4ºF), or signs or symptoms suggestive of CRS or neurotoxicity for close monitoring of cardiac and organ function, including routine neurologic exams. In addition, febrile subjects need to be worked up for infections per institutional guidelines.

Subjects who do not have adequate social support (a full-time caregiver) outside of the hospital or do not have reliable transportation to the clinic for scheduled evaluations or emergencies post-therapy should be considered for hospitalization for the first 30 days following JCAR017 infusion.

Subjects **should not** experience a significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with JCAR017 infusion. Subjects who meet at least one of the following criteria on the day of scheduled JCAR017 infusion should have JCAR017 administration delayed:

- Suspected or active systemic infection
- Onset of fever ≥ 38°C/100.4°F, not related to underlying disease
- Presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New onset or worsening of other non-hematologic organ dysfunction ≥ Grade 3
- Taking any of the prohibited medications as described in Section 8.2

Subjects with active infection must have JCAR017 infusion postponed until the active infection has resolved (subjects with suspected/active infection must have negative culture for at least 24 hours on appropriate antibiotics or negative rapid viral panel). Subjects with non-hematologic organ toxicities may not receive JCAR017 until the non-hematologic organ toxicities have recovered to ≤ Grade 2. In case of a possible delayed infusion, discussion with medical monitor must occur regarding decision on delay of treatment and/or repeating of LD chemotherapy.

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

The following will be performed on Day 1 **prior** to JCAR017 infusion:

- IRT registration
- Physical examination
- Tanner staging
- Weight
- Vital signs (measured within 15 minutes prior to the first JCAR017 administration, and approximately every 15 minutes thereafter for the first hour, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the final IV administration, vital signs should be monitored as clinically indicated until stable)
- Karnofsky (subjects ≥ 16 years of age) or Lansky (subjects < 16 years of age) performance status assessment
- Routine neurologic examination
- Record all AEs and associated concomitant medications
- Administration of PedsQL questionnaires (subject and parent/caregiver as applicable)
- Hospital resource utilization
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
- JCAR017 premedication (see Section 7.2.2)
- Research peripheral blood samples [redacted]
  - For JCAR017 PK [redacted]

6.2.1.4. Days 2, 3, and 4 (+1 day for Day 4)

- Vital signs
- Routine neurological examination
- Physical examination
- Record all AEs and associated concomitant medications
- Hospital resource utilization
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry

  - Hematology
  - Coagulation
  - Inflammatory markers
- Research peripheral blood samples [redacted]
  - For JCAR017 PK [redacted] (Day 2 and Day 4 only)

6.2.1.5. Day 7 (±1 day)

- Physical examination
- Vital signs
- Karnofsky (subjects ≥ 16 years of age) or Lansky (subjects < 16 years of age) performance status assessment
- Routine neurological examination
- Record all AEs and associated concomitant medications
- Hospital resource utilization
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
- Research peripheral blood samples [redacted]:
  - For JCAR017 PK [redacted]

6.2.1.6. Day 10 (±1 day)

- Vital signs
- Physical examination
- Routine neurologic examination
- Record all AEs and associated concomitant medications
- Hospital resource utilization
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers

- Research peripheral blood samples [redacted]
  - For JCAR017 PK [redacted]

6.2.1.7. Days 14, 21, 28, and 56

- Physical examination
- Tanner staging on Days 28 and 56
- Vital signs
- Karnofsky (subjects ≥ 16 years of age) or Lansky (subjects < 16 years of age) performance status assessment
- Routine neurologic examination
- Record all AEs and associated concomitant medications
- Administration of PedsQL questionnaires (subject and parent/caregiver as applicable) required on Days 28 and 56
- Hospital resource utilization
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers (required on Days 14 and 21; required on Days 28 and 56 if clinically indicated)
  - Immunoglobulins
- Cerebrospinal fluid assessment is required for subjects with suspected or confirmed CNS involvement (not required after PD/relapse occurs). CNS imaging should be performed as clinically indicated.
- Research peripheral blood samples [redacted]:
  - [redacted]
  - JCAR017 PK [redacted] required on Days 14, 21, 28, and 56
  - [redacted]
- Response evaluation by local Investigator review and Independent Review Committee (IRC)

  B-ALL subjects ONLY (Day 28 and 56):
  - Bone marrow morphological assessment (BM aspirate [BM biopsy only if clinically indicated])
  - Peripheral blood morphological assessment (PB smear)

– Minimal residual disease analysis

B-NHL subjects ONLY (Day 28):

– CT/MRI

– Tumor biopsy (for subjects with accessible disease)

– Bone marrow morphological assessment (BM aspirate [BM biopsy only if clinically indicated]) only if previous BM involvement at screening

Please refer to Section 6.10 for additional details on B-ALL and B-NHL efficacy assessments.

6.2.2. Post-treatment Follow-up Period

All subjects who received any JCAR017 infusion should complete the Post-Treatment Follow-up period visits at approximately 3, 6, 9, 12, 18, and 24 months (EOS) after JCAR017 infusion for disease status and survival.

The following assessments will be performed at each of the Post-Treatment Follow-up visits in subjects who have not received subsequent anticancer treatment:

- IRT registration (EOS visit)
- Physical examination and Tanner staging
- Routine neurologic examination
- Karnofsky (subjects ≥ 16 years of age) or Lansky (subjects < 16 years of age) performance status assessment
- Cerebrospinal fluid assessment is required for subjects with suspected or confirmed CNS involvement (not required after PD/relapse occurs). CNS imaging should be performed as clinically indicated.
- Response evaluation by local Investigator review and IRC – at timepoints indicated in Table 3

  B-ALL subjects ONLY:

  – Bone marrow morphological assessment (BM aspirate [BM biopsy only if clinically indicated])

  – Peripheral blood morphological assessment (PB smear)

  – Minimal residual disease analysis

  B-NHL subjects ONLY:

  – CT/MRI

  – Tumor biopsy for subjects with accessible disease only required as clinically indicated

  - Bone marrow morphological assessment (BM aspirate [BM biopsy only if clinically indicated]) required as clinically indicated if BM involvement at screening

  Please refer to Section 6.10 for additional details on efficacy assessments.

- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Immunoglobulins (not required if B-cell recovery documented without recent administration of intravenous immunoglobulins [IVIG])
- Research peripheral blood samples [redacted]:
  - [redacted]
  - [redacted]
  - JCAR017 PK [redacted] (required at all Post-treatment Follow-up Period timepoints). [redacted]
  - [redacted]
- Record all AEs and associated concomitant medications according to Table 8 and Table 7, respectively.
- Administration of PedsQL questionnaires (subject and parent/caregiver as applicable)
- Hospital resource utilization
- Survival status

The following assessments will be performed in subjects who have received subsequent anticancer treatment:

- Collection of anticancer treatment since JCAR017 infusion
- Physical examination at Months 12 and 24
- Immunoglobulins per Table 3 (not required if B-cell recovery documented without recent administration of IVIG)
- [redacted]
- JCAR017 PK [redacted] (required at all timepoints). [redacted]
- Survival status

Note: Subjects who receive HSCT post-JCAR017 (but no other subsequent anticancer treatment) should continue to undergo response/efficacy evaluations as described above (B-ALL or B-NHL), unless they have demonstrated relapse/PD prior to HSCT.

6.3. Unscheduled Evaluations

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

- Physical examination
- Neurological examination
- Vital signs
- Karnofsky (subjects ≥ 16 years of age) or Lansky (subjects < 16 years of age) performance status assessment
- Clinical laboratory evaluations
- CT/MRI scan
- MUGA scan/ECHO
- CD19+ status
- Tumor biopsy (see the JCAR017-BCM-004 laboratory manual)
- Bone marrow assessment (see the JCAR017- BCM-004 laboratory manual)
- Peripheral blood smear (see the JCAR017-BCM-004 laboratory manual)
- Cerebrospinal fluid assessment (see the JCAR017-BCM-004 laboratory manual)
- Research peripheral blood samples [redacted]:
  - [redacted]
  - JCAR017 PK [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

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

- Lumbar puncture for CSF assessment
- Pleural, peritoneal, or other relevant fluid sampling
- Tissue sampling

- Autopsy

6.4. Assessments at Time of Death (Subjects Receiving JCAR017)

In case an autopsy is performed and if feasible, blood and tissue samples will be collected for central analysis of markers related to safety and efficacy of the CAR T cells. See the JCAR017-BCM-004 laboratory manual for details.

6.5. Early Withdrawal

If a subject voluntarily withdraws prematurely from the study, a visit will be scheduled as soon as possible, and all of the assessments listed for the 24-month (EOS) visit will be performed. For subjects receiving LD chemotherapy but not JCAR017, all AEs will be collected for 30 days following the last dose of LD chemotherapy.

6.6. Second Primary Malignancies Follow-up Period

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancies, regardless of causal relationship to JCAR017, occurring throughout the subject's entire participation in the study. If a subject develops a second primary malignancy, Celgene will request that a tumor sample, BM and blood samples are collected (refer to JCAR017-BCM-004 laboratory manual). See also [redacted] Section 6.11.1.

6.7. Survival Status

All subjects will be followed for survival for 2 years after JCAR017 infusion in the Post-Treatment Follow-up Period which starts after Day 56 and continues for 2 years after JCAR017 infusion. Additional survival follow-up information will be collected in the context of the LTFU protocol once a subject (who received JCAR017) is discontinued from the study.

6.8. Long-Term Follow-up

Because this protocol involves gene transfer, long-term follow-up for lentiviral vector safety, disease status for at least 5 years, second primary malignancies and survival will continue after EOS under a separate LTFU protocol thereafter for up to 15 years after the JCAR017 infusion (European Medicines Agency [EMA], 2009; FDA, 2010; FDA, 2006). In addition, details on all subsequent anti-neoplastic treatments for at least 5 years must be documented. Note: The long-term follow-up may exceed 15 years if the subject does not achieve Tanner Stage 5 by the end of the 15-year safety follow-up period.

All subjects who either complete the Post-Treatment Follow-up Period specified in this protocol or who prematurely withdraw after JCAR017 infusion will be asked to enroll in the LTFU protocol at the EOS visit or at the time of withdrawal, respectively. A separate ICF/IAF 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, if permitted by local regulations.

6.9. Safety Assessments

6.9.1. Physical Examination

A physical examination will be conducted as specified timepoints indicated in the schedule of events (Table 3). Examinations should include assessments of the following body parts/systems: abdomen, extremities, heart, lungs, and neurological.

At screening, pre-treatment and at each visit for response assessment, the physical exam must also include an assessment of the presence of extramedullary disease (ie, hepatomegaly, splenomegaly, lymph nodes, CNS, skin/gum infiltration, testicular masses and other disease manifestations).

Significant physical exam findings identified during screening should be recorded in the medical history CRF. The disease response assessment results, including presence or absence and physical location of extramedullary disease, will be recorded in the appropriate eCRF. Significant abnormalities that begin or worsen after initiation of study treatment must be recorded as AEs, as defined in Section 10.

6.9.2. Tanner Staging

Growth, development, and sexual maturity assessments will be included in the physical examination using the Tanner staging system (Marshal and Tanner, 1969 and 1970). Once a subject reaches an overall Tanner Stage of 5, subsequent Tanner Staging assessments do not need to be performed. If a subject is Tanner Stage 5 at screening, only the screening Tanner Staging is required to be performed.

6.9.3. Vital Signs

Vital signs include temperature, respiratory rate, heart rate, blood pressure, and oxygen saturation via pulse oximetry (SaO_2).

6.9.4. Height and Weight

Height in centimeters (cm) or inches (in) and body weight to the nearest kg.

6.9.5. Routine Neurologic Examinations

A routine neurologic examination should include, at minimum, a physical examination to assess cranial nerves, motor and sensory skills, coordination and balance.

6.9.6. Cerebrospinal Fluid Assessment and Central Nervous System Symptom Assessment

Cerebrospinal fluid assessment is required to be performed for subjects with suspected or confirmed CNS involvement at screening. Repeated CSF assessments should be performed if CNS involvement is suspected or confirmed at the pre-treatment evaluation or at any time during the study as clinically indicated (eg, if new CNS symptoms occur, or if clinical signs or suspicion of CNS involvement exist). Cerebrospinal fluid assessments (post JCAR017 infusion) are not required for subjects in CR/CRi following JCAR017 administration, unless suspicion of CNS relapse. Sampling of CSF will be performed per institution's clinical guidelines and analyzed for

cell count, differential cytology, protein level and for research analysis (see the JCAR017-BCM-004 laboratory manual for instructions on sending a sample for central JCAR017 testing). Cerebrospinal fluid cultures (bacterial, fungal, viral) should be performed as clinically indicated for suspicion of infection.

CNS imaging (CT and/or MRI) scans should also be performed as clinically indicated with CAR T related neurotoxicity.

The classification of CNS status includes the following (NCCN, 2019):

- CNS-1 refers to no lymphoblasts in the CSF regardless of WBC count;
- CNS-2 is defined as WBC less than 5/mcL in CSF with presence of lymphoblasts;
- CNS-3 is defined as WBC of 5/mcL or greater with presence of lymphoblasts or clinical symptoms (ie, cranial nerve palsy, clinical spinal cord compression, or isolated intracerebral mass)

CNS remission is defined as achievement of CNS-1 status in a subject with CNS-2 or CNS-3 at baseline assessment (prior to LD chemotherapy).

CNS relapse is defined as development of CNS-3 status (if < CNS-3 at baseline) or development of clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome, etc.). If clinical signs of CNS leukemia/lymphoma exist, it must be confirmed by relevant methods (eg, biopsy, lumbar puncture, CNS imaging [CT or MRI of brain], etc.) to define CNS relapse.

6.9.7. Performance Status

The Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status will be used to evaluate subject eligibility at screening and will be assessed throughout the study.

The same performance status scale used at screening should continue to be assessed during the duration of the study, regardless of any age change.

6.9.8. Echocardiogram/Multi-Gated Acquisition Scan

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

6.9.9. Electrocardiogram

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

[redacted]

6.9.11. Clinical Laboratory Evaluations

Screening and other laboratory evaluations will be performed both centrally and locally according to Table 3 and Appendix D. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs/SAEs or expected events. Clinical management of study subjects will be based on local assessments.

It is the responsibility of the Investigator to obtain and review laboratory results for subject safety and follow up with subjects in a timely manner.

6.10. Efficacy Assessment

The key efficacy assessments to be measured include peripheral blood count, BM, CSF, physical examination, evaluation of CNS symptoms, disease specific imaging (ie, CT or MRI), and B-symptoms (ie, NHL). Peripheral blood and BM will be analyzed locally and also sent to a central laboratory for morphologic evaluation and determination of MRD status (ie, B-ALL).

Overall response will be evaluated locally by the Investigator and by an Independent Review Committee (IRC). The central laboratory results, imaging and pertinent clinical data will be provided to the IRC, who will provide a separate response assessment. Clinical management of study subjects will be based upon Investigator's assessment. Efficacy based endpoints (primary and secondary) will be based on the IRC review.

All components of a disease assessment must be performed within 14 days of each other to qualify as the same response evaluation, unless otherwise specified.

6.10.1. Acute Lymphoblastic Leukemia (B-ALL)

Efficacy assessments for B-ALL subjects will be performed according to the 2019 National Comprehensive Cancer Network (NCCN) response criteria guidelines for pediatric ALL (Appendix B). A full response evaluation, including assessments of peripheral blood, BM,

CSF/CNS assessment (if applicable), and physical exam including assessment of extramedullary disease is required at screening, pre-treatment and at each response assessment. Disease assessment at the pre-treatment visit (prior to LD chemotherapy) will serve as the baseline. Subjects will be retrospectively reassigned to the appropriate cohort should their pre-LD chemotherapy disease status show a change from the screening.

The first disease assessment will be performed 28 days after JCAR017 infusion. If the subject cannot be assessed for CR/CRi due to hypoplastic marrow, a repeat marrow examination should be performed when there is evidence of hematopoietic recovery so that remission can be assessed for the first time. Repeat BM examinations and response assessments will be performed at Day 56, Day 90 and at relapse and/or as clinically indicated.

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, BM, CSF and extramedullary disease assessment (where applicable) confirmed at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. Any additional assessments performed for the purpose of disease response evaluation must also support a response of remission.

6.10.1.1. Minimal Residual Disease (MRD)

Minimal residual disease in B-ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods and will be assessed on all B-ALL BM timepoints by a validated assay at a central analytical laboratory. For Cohort 2 in Phase 2, MRD results will be used for enrollment and monitoring of subjects for the primary endpoint.

- MRD relapse will be defined as an MRD detection by validated assay at a frequency of 1×10^{-4} or greater in BM cells following an initial MRD negative (less than 1×10^{-4}) CR/CRi.

Subjects who demonstrate morphologic remission and are MRD negative upon restaging prior to initiation of lymphodepleting therapy will continue to be treated and followed on study but will not be considered evaluable for the MRD response endpoints and may be replaced.

6.10.2. Non-Hodgkin Lymphoma (B-NHL)

Efficacy assessments will be performed according to the 2015 international pediatric NHL response criteria guidelines (Appendix C) based on radiographic tumor evaluation by CT/MRI scans (chest, neck, abdomen and pelvis). Radiographic response determination will be evaluated locally at the site and also sent for central radiology review. Bone marrow aspirates/biopsies and tumor biopsies will also be performed according to Table 3 to assess involvement by lymphoma and will be considered when determining overall response. Efficacy assessments will be performed at Day 28, 90, 180, 270 and at relapse/PD/as clinically indicated.

B-NHL subjects who do not receive anticancer treatment control while JCAR017 is being manufactured will have CT/MRI scans repeated (within 7 days prior to start of LD chemotherapy), only if no scans were done at screening or within 3 weeks prior to the start of LD chemotherapy, to evaluate the tumor load. If the subject has previous imaging within 14 days of screening that is after the last relapse/progression and no anticancer treatment was given between the imaging and screening, these scans can be used as the baseline assessment.

6.10.2.1. Pseudoprogression

If a subject with B-NHL demonstrates early tumor progression (defined as occurring prior to/at 1 month after JCAR017 infusion), the Investigator is responsible for evaluating whether the subject is experiencing a possible pseudoprogression (ie, tumor flare, which is a local inflammatory reaction indicating early tumor response at sites of disease such as lymph nodes.

6.10.3. Independent Review Committee

An IRC will be established to review the BMA/BMB, peripheral blood and radiographic data provided by the central laboratory as well as pertinent clinical eCRF data listings (as appropriate) in order to perform an independent response assessment. Clinical management of study subjects will be based upon local Investigator's assessment. The designation of response for the primary and select secondary based endpoints will be based only on the evaluations made by the IRC. An IRC charter will detail the IRC data flow and review process in alignment with the response definitions in Appendix B and Appendix C. Results from the IRC will not be provided to the clinical sites.

6.11. Pharmacokinetics

Assessment of JCAR017 PK will be determined by droplet digital polymerase chain reaction (ddPCR) [redacted]

Detailed information regarding the collection, handling, and shipment of PK assessment samples is provided in the JCAR017-BCM-004 laboratory manual.

6.11.1. Viral Vector Sequence Pharmacokinetic Testing

Persistence of JCAR017 vector sequences will be monitored. Details regarding sample collection and processing are provided in the JCAR017-BCM-004 laboratory manual. [redacted].

At any time point ≥ 12 months after JCAR017 infusion, if persistence vector sequence is detected in ≥ 1% of cells in two consecutive blood samples, the pattern for vector integration sites will be analyzed. If integration pattern suggests a predominant integration site, a repeat analysis will be conducted within 3 months and further studies including insertion site analysis will be performed.

Any observation of clonal outgrowth (clonal dominance), or monoclonality, will be reported as an SAE within 24 hours.

If a subject develops a second primary malignancy, Celgene will request a sample for assessment of viral vector sequence testing.

[redacted]

[redacted]

6.13. Patient-reported Outcomes

Patient-reported quality-of-life outcomes will be administered according to Table 3.

The Pediatric Quality of Life (PedsQL) Core module, Cancer module, and Multidimensional Fatigue Scale will be used to assess the subject's health as well as physical, social, emotional, and school functioning. The parent versions of the same modules will be administered to the parent/caregivers. The PedsQL Family Impact Module will also be administered to caregivers through the EOS (will not be administered in the LTFU protocol).

In this study, completion of the following questionnaire(s) will be required based on age at study entry as described in Table 5:

Table 5: Administration of Pediatric Quality of Life Inventory Questionnaires

Age at Study Entry	PedsQL™ 4.0 Version
0 to 1	Not Done[a]
2 to 4	Parent/caregiver proxy version only[a]
5 to 7	PedsQL (Young Child)
8 to 12	PedsQL (Children)
13 to 17	PedsQL (Teens)
18 to 25	PedsQL (Young Adult)

[a] Subjects less < 5 years of age will not have self-questionnaires administered. Only parent/caregiver proxy version and Family Impact module will be completed of subjects ages 2 to 4 years of age.

The questionnaire will be completed by the subjects/caregivers before they see the Investigator, or any clinical assessments are performed at any given visit. Under extenuating circumstances where the questionnaire(s) were not completed at the screening visit, it must be completed before administration of LD chemotherapy.

Questionnaires should be completed in the language most familiar to each subject, and subjects/caregivers should be given adequate time and space to complete the questionnaires. For each visit a questionnaire is to be performed, it is expected to have the subject (self-administering where applicable), parent-proxy and Family Impact modules completed. If possible, the subject/caregiver should first complete the PedsQL Core module and then complete any additional modules.

Parents/caregivers, Children (age 8-12), Teens (age 13-17) and Young Adults (age 18 to 25) may self-administer the PedsQL after introductory instructions from the administrator. If the administrator determines that the subject is unable to self-administer the PedsQL (eg, due to illness, fatigue, reading difficulties), the PedsQL should be read aloud to the subject. However, the administrator and the caregivers should be instructed not to modify or interpret subjects' responses, but to record them exactly as they were produced by the subject.

Age-appropriate versions of the questionnaires will be administered and a 30 day recall assessment will be utilized. Administers of the questionnaire should make the decision about age appropriateness. If it is felt the subject will or has difficulty understanding the age-appropriate version, the preceding age group version may be administered. However, if the subject presents with severe cognitive impairments (as determined by the administrator), the PedsQL may not be appropriate. In such cases, only the Parent-Proxy Report and Family Impact Module should be administered to the child's parent/caregiver and this decision should be source documented. In addition, the parent/caregiver and subject should complete the questionnaires independently of one another. The parent/caregiver, subject, and/or other family members should be discouraged from consulting with one another during the completion of the questionnaire.

Subjects/caregivers should be administered the same version of the questionnaires for the first year on study, despite a change in age range. After the first year on study, an updated version of the questionnaires should be administered to reflect any change in age. Once a subject enrolls into the LTFU protocol, an updated version of the questionnaires should be administered based on the subject's age at the time of the assessment.

Site personnel should review questionnaires for completeness and ask subjects/caregivers to complete any missing responses. Reasons for missing reported outcome questionnaires should also be captured so that the appropriate imputation method can be employed to correct for missing data in the analysis. If subjects/caregivers refuse to complete all or any part of a questionnaire, this will be documented. 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.

Completed questionnaire(s) and any unsolicited comments should be reviewed and assessed by the Investigator for responses which may indicate potential AEs, including SAEs, before any clinical study assessments. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the subject to change responses reported in the completed questionnaires.

6.14. Hospital Resource Utilization

Hospital resource utilization will be assessed based on the numbers of hospitalizations, intensive care unit (ICU) inpatient days and non-ICU inpatient days in addition to outpatient visits. Dates of admission and discharge to the hospital and to the ICU will be collected together with the reasons for the hospitalization(s).

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product

7.1.1. JCAR017

See Section 1.2.3 for a description of JCAR017.

JCAR017 will be supplied by Celgene and labeled appropriately as IP for this study. See the JCAR017 Product Administration Manual for details of packaging and labeling, product request and shipment, product preparation and administration, and product disposal and destruction.

7.2. Treatment Administration and Schedule

7.2.1. Lymphodepleting Chemotherapy

Subjects will be treated for 3 days with fludarabine IV (30 mg/m^2/day) and cyclophosphamide IV (300 mg/m^2/day) prior to JCAR017 infusion. Lymphodepleting chemotherapy should be initiated so as to be completed 2 to 7 days before JCAR017 infusion.

See Section 1.3.3.2 for a description of the LD chemotherapy dose.

Please refer to local fludarabine and cyclophosphamide prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of fludarabine and cyclophosphamide (see current version of Prescribing Information).

Serum creatinine will be measured on the first day of LD chemotherapy; LD chemotherapy should be withheld if serum creatinine is beyond the maximum value (see Section 4.2) using the Schwartz formula or radioisotope GFR is $\leq$ 70 mL/min/1.73 m^2.

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

If side effects from the LD chemotherapy occur, JCAR017 infusion may be delayed for up to 14 days after LD chemotherapy upon discussion with Celgene. If the delay is more than 14 days, some of the screening procedures as well as LD chemotherapy may need to be repeated (Refer to Section 6.1). Refer to Section 6.2.1.2 for the assessments that will be performed on each day of LD chemotherapy.

7.2.2. JCAR017 Premedication

Subjects should be premedicated with paracetamol/acetaminophen 12.5 mg/kg (maximum dose 650 mg) by mouth (per os [PO]) or IV at an equivalent dose and diphenhydramine hydrochloride 1 milligram (mg)/kg (maximum dose 50 mg) PO or IV 30 to 60 minutes prior to JCAR017 infusion. If diphenhydramine hydrochloride is not commercially available or a subject cannot tolerate diphenhydramine hydrochloride, premedication with an equivalent antihistamine may be substituted. Ondansetron 0.15 mg/kg (maximum dose 8 mg) PO or IV may be optionally used prior to JCAR017 infusion.

These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Premedication with steroids should be avoided.

7.2.3. JCAR017 Preparation and Cell Thawing

See the JCAR017-BCM-004 Product Administration Manual for details.

7.2.4. JCAR017 Administration

Each JCAR017 dose consists of a single infusion of two individually formulated CD4+CAR+ and CD8+CAR+ T cell suspensions administered separately in a 1:1 ratio in a formulation containing dimethyl sulfoxide (DMSO). The subject must be continuously monitored during IV administration of JCAR017. Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry) will be measured within 15 minutes prior to the first JCAR017 administration, and approximately every 15 minutes thereafter for the first hour, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the completion of IV administration, vital signs should be monitored as clinically indicated until stable.

See the JCAR017 Product Administration Manual for complete information.

7.2.5. JCAR017 Dose Levels and Schedule

JCAR017 will be given on Day 1 (2 to 7 days after completion of lymphodepleting chemotherapy).

7.2.5.1. Phase 1

Up to 5 dose levels of JCAR017 will be evaluated (Table 6).

Enrollment will commence in pediatric subjects at DL1 of $0.05x10^6$ CAR+ T cells/kg (maximum dose of $5x10^6$ JCAR017 CAR+ T cells [non-weight adjusted]). If this dose is confirmed to be safe and tolerable, additional pediatric subjects will be enrolled at higher dose(s) up to $0.75 x10^6$ CAR+ T cells/kg (maximum of $75x10^6$ JCAR017 CAR+ T cells [non-weight adjusted]) with the aim to identify the RP2D. Dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm (Guo, 2017) as described in Section 3.1. Based on the cumulative safety, PK and preliminary efficacy data, a recommended pediatric dose to be further tested in the Phase 2 portion of the trial will be selected in consultation with the SRC based on data from at least 10 pediatric subjects treated at this RP2D level. Analysis of the JCAR017 manufactured product may also be considered.

Table 6: JCAR017 Dose Levels

Dose Level	JCAR017 Dose	JCAR017 Maximum Dose[a]
1[b]	0.05 x 10^6 CAR+ T cells/kg	5 x 10^6 CAR+ T cells
2	0.15 x 10^6 CAR+ T cells/kg	15 x 10^6 CAR+ T cells
3	0.30 x 10^6 CAR+ T cells/kg	30 x 10^6 CAR+ T cells
4[c]	0.50 x 10^6 CAR+ T cells/kg	50 x 10^6 CAR+ T cells
5[c]	0.75 x 10^6 CAR+ T cells/kg	75 x 10^6 CAR+ T cells

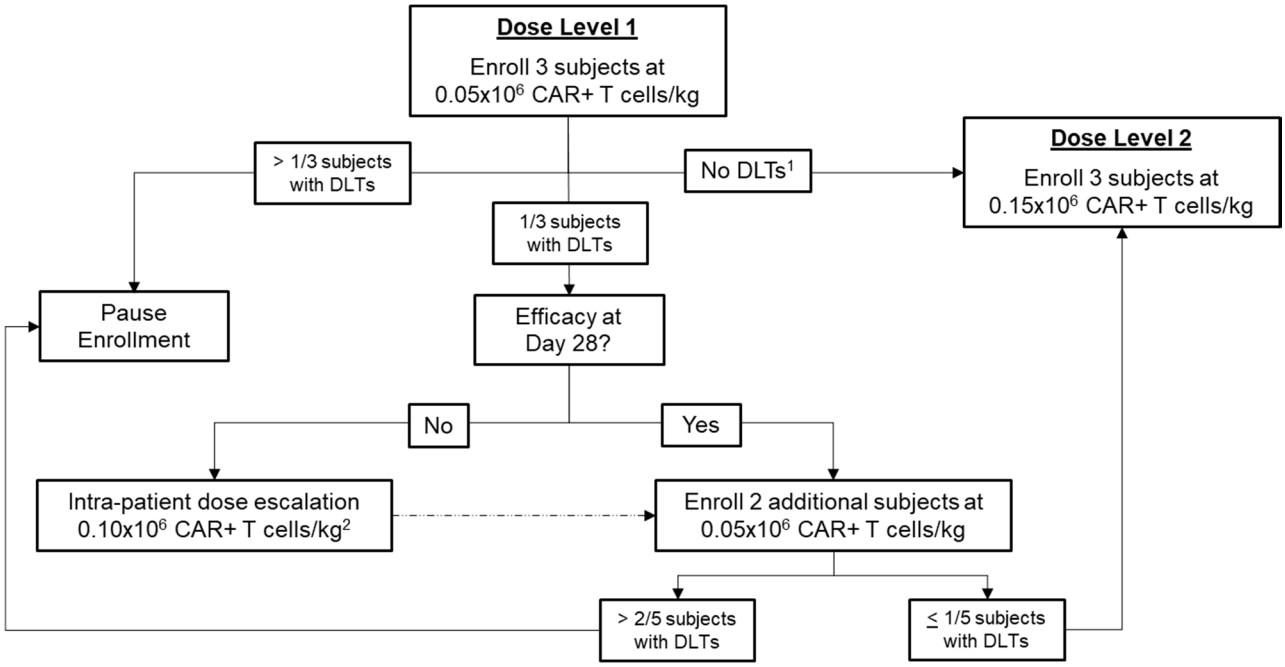
[a] JCAR017 dosing will be capped at 100kg for all dose levels.
[b] Dose escalation will proceed as described in Figure 3.
[c] Optional based on comprehensive assessment.

7.2.5.1.1. mTPI-2 Dose Escalation Decision Pathway (Dose Level 1 Only)

Dose de-escalation from DL1 is not currently planned. Therefore, dose escalation from DL1 to DL2 will follow a modified mTPI-2 algorithm as described in Figure 3. Enrollment will be temporarily suspended and reviewed by Celgene with input from SRC and only if needed, from the DSMB and Study Steering Committee (SSC) when:

- > 1 subject with a DLT occurring within the first 3 DLT-evaluable subjects at a JCAR017 dose of $0.05x10^6$ CAR+ T cells/kg, or
- > 2 subjects with DLTs occurring across the first 5 total DLT-evaluable subjects at a JCAR017 dose of $0.05x10^6$ CAR+ T cells/kg

Figure 3: mTPI-2 Dose Escalation Decision Pathway for Dose Level 1 Only



Abbreviations: CAR = chimeric antigen receptor; DLT = dose limiting toxicity

[1] Subjects without response are eligible for intra-patient dose escalation.

[2] For subjects without DLT at DL1, see Section 7.2.5.1.2.

7.2.5.1.2. Intra-Patient Dose Escalation

If additional JCAR017 doses are available, a one-time retreatment with intra-patient dose-escalation of $0.10x10^6$ CAR+ T cells/kg (maximum dose of $10x10^6$ JCAR017 CAR+ T cells [non-weight adjusted]) will be allowed for subjects at DL1 who have not experienced severe toxicity and have no response on Day 28 after JCAR017 infusion. The subject must continue to meet the eligibility criteria for initial therapy with JCAR017. Data from subjects who are retreated with JCAR017 will not be included in the mTPI-2 algorithm to estimate DLT rates at DL2.

Subjects will follow the schedule of assessments for screening (some assessments may not be required after discussion with Celgene) and upon meeting eligibility criteria, pre-treatment

evaluations will begin. Post-treatment follow-up will occur per the schedule of assessments from the time of the last dose of JCAR017and will continue for 2 years after the last dose of JCAR017, unless the subject is lost to follow-up.

Retreatment and/or intra-patient dose escalation of JCAR017 will not be allowed at other dose levels.

7.2.5.2. Phase 2

The identified RP2D from Phase 1, will be applied in Phase 2 (Cohort 1, Cohort 2 and Cohort 3). Subjects 18 to 25 years of age may enroll in Phase 2 and will be treated with JCAR017 at the RP2D.

7.2.6. Definition of Dose-limiting Toxicity

Dose-limiting toxicities will be evaluated for the subjects in Phase 1 during the DLT evaluation period of 28 days after JCAR017 infusion. The severity grading of adverse events will be determined according to NCI CTCAE Version 4.03. Cytokine release syndrome is graded as per Table 10.

A DLT will be defined as below:

- Death not related to disease progression
- Grade 4 neurotoxicity
- Grade 3 neurotoxicity of greater than 7 days' duration
- Grade 3 neurotoxicity that does not revert to baseline within 28 days of the start date of the Grade 3 event
- Seizures of any grade that do not resolve within 7 days
- Grade 4 CRS that does not resolve to Grade ≤ 3 within 3 days
- Grade 3 CRS that does not resolve to Grade ≤ 2 within 7 days
- Any increase in aspartate aminotransferase (AST) or ALT $> 3 \times$ ULN and concurrent increase in total bilirubin $> 2 \times$ ULN that is unrelated to CRS and has no other probable reason to explain the combination of increases
- Any cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic Grade 3 or 4 event not pre-existing or not due to the underlying malignancy
- Any other Grade 3 or 4 event deemed unexpected by the Investigator and considered a DLT upon evaluation by the SRC

Should a subject experience a suspected DLT, the treating Investigator should contact Celgene's medical monitor prior to declaring the event a DLT. All DLT cases will also be discussed with the SRC during regular calls with sites and their respective investigators aiming to review and share all safety related events including but not limited to DLTs.

Please see Section 10 for further details on AE reporting.

7.2.7. Overdose

Overdose, as defined for this protocol, refers to fludarabine, cyclophosphamide or JCAR017. On a per-dose basis, an overdose is defined as the following amount over the protocol-specified dose of these drug(s) assigned to a given subject, regardless of any associated AEs or sequelae:

- IV: 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster or slower than the protocol-specified infusion time reflected as infusion time (± 50%).

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the electronic case report form (eCRF) (see Section 10.1 for the reporting of AEs associated with overdose).

[redacted]

7.3. Method of Treatment Assignment

Interactive response technology (IRT) will be employed to manage cohort assignments. IRT registration will be performed according to Table 3.

7.4. Packaging and Labeling

7.4.1. Product Tracking

7.4.1.1. Lymphodepleting Chemotherapy

Manufacturer details and batch numbers will be used for the products tracking.

7.4.1.2. JCAR017

The identity of the IP will be checked and verified at each critical step of cell processing as part of the chain of identity. 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, JCAR017 manufacturing and testing, in-process labeling, and JCAR017 labeling and packaging for shipment.

7.4.2. Product Packaging and Labeling

7.4.2.1. Lymphodepleting Chemotherapy

Fludarabine and cyclophosphamide will be provided by the clinical sites and labeled as per their local procedures.

7.4.2.2. JCAR017

The label(s) for the IP will include, but may not be limited to, Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

These same identifiers are maintained from leukapheresis collection throughout the manufacturing process and are used on the final JCAR017 cell product. These unique identifiers should be verified per the Chain of Identity procedures listed in the JCAR017 Product Administration Manual.

The final JCAR017 cell product is provided cryopreserved and packaged to the study site per the dosing regimen specified in the protocol.

Prior to the JCAR017 infusion, two trained individuals will verify all unique identifier information in the presence of the subject/guardian(s) to confirm that the information is correctly matched to the subject.

7.4.3. Cell Product Supply and Storage

Detailed instructions on the storage, handling, and preparation of JCAR017 cell product will be provided in the JCAR017 Product Administration Manual.

7.5. Investigational Product Accountability and Disposal

7.5.1. Accountability Procedures

Inventory must be performed, and a product receipt log must be filled out and signed by the person accepting the shipment of JCAR017 cell product.

7.5.2. Drug Disposal and Destruction

Celgene (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6. Investigational Product Compliance

The administered dosage of JCAR017 will be recorded in source documents. The Investigator(s) or designee is responsible for taking an inventory of each shipment of IP received and comparing it with the accompanying shipping order/packaging slip. The Investigator(s) will verify the accuracy of the information on the shipping order/packaging slip.

At the study site, the IP will be stored in a locked, safe area to prevent unauthorized access and should be stored as directed on the product label.

An accurate accounting of the dispensing and return of IP for each study subject will be maintained in source documents on an ongoing basis by a member of the study site staff.

Additionally, if any IP is lost or damaged or if the study subject misses a dose, this information should be documented in the study subject's eCRF and source documents.

Celgene will instruct the Investigator on the return, disposal, and/or destruction of unused IP.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

8.1. Permitted Concomitant Medications and Procedures

Medications and procedures will be recorded as shown in Table 7. 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.

Table 7: Reporting Periods for Concomitant Medications

Start	End	Required Reporting
Informed Consent	Initiation of LD chemotherapy	Medications taken by the subject at the time of an AE related to protocol-mandated procedures or for active medical history conditions
Start of LD chemotherapy	Day 90, after JCAR017 infusion	All medications
Day 91, after JCAR017 infusion	End of study	Only medications ongoing at the time of AEs related to any protocol-mandated procedures or JCAR017

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

Due to the large amount of data generated during hospitalizations, a targeted concomitant medication collection approach will be utilized for the eCRF. The following medications should NOT be entered on the Concomitant Medications eCRF during inpatient and ICU stays (also defined in the eCRF Completion Guidelines):

- IV fluids (with the exception of IV fluids administered for treatment of hypotension associated with CRS, which should be recorded)
- Heparin flushes
- Stool softeners
- Vitamins, minerals, health supplements
- Saline flushes
- Lotions

The following treatments should be reported during inpatient and ICU stays:

- Vasopressor – enter the maximum infusion rate/day
- Oxygen – enter the maximum fraction of inspired oxygen (FiO_2) per day
- Transfusions
- Antibiotics
- Growth factors

- Systemic anticoagulants

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatment or disease progression. Supportive care, including, but not limited to antiemetic medications, may be administered at the discretion of the Investigator.

Prophylactic treatment/measures are strongly recommended for subjects at risk for tumor lysis syndrome (TLS), per institutional or clinical standards. The use of red blood cells and platelet transfusions, and/or colony-stimulating factors is permitted per institutional or clinical standards. Use of colony-stimulating factors should be avoided in B-ALL subjects before Days 28 and 56 to not interfere with the BM interpretation.

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

For information regarding other drugs that may interact with JCAR017 and affect its metabolism, pharmacokinetics, or excretion, please see the IB and/or local package insert.

Vaccination with a killed vaccine is permitted at any time in consultation with the medical monitor.

8.1.1. Anticancer Treatments between Leukapheresis and Lymphodepleting Chemotherapy

If necessary, anticancer treatment is allowed for disease control while JCAR017 is being manufactured (ie, after leukapheresis and prior to LD chemotherapy). Chemotherapy is allowed if completed at least 7 days prior to the start of LD chemotherapy. If other agents are used, the washout periods noted in the exclusion criteria (see Section 4.3) must be met. The use of therapeutic agents with little/no evidence in the scientific literature for B-ALL or B-NHL should be discussed with Celgene. For B-NHL subjects, local radiation is allowed to a single lesion or subset of lesions.

8.2. Prohibited Concomitant Medications and Procedures

The following medications are prohibited until lack of response, subsequent therapy, or 1 year following JCAR017 infusion, whichever comes first:

- Steroids: therapeutic doses (> 0.4 mg/kg [maximum 20 mg/day] of prednisone or equivalent) unless used for treatment of CRS. Therapeutic doses may be used in life-threatening situations and for other medical conditions when indicated, or after loss of detectable JCAR017 cells. Pretreatment containing steroids may be given for necessary medications (eg, IVIG) after discussion with Celgene. Premedication with steroids for JCAR017 infusion is not allowed. Physiologic replacement dosing of steroids ($\leq$ 12 mg/m^2/day hydrocortisone or equivalent [$\leq$ 3 mg/m^2/day prednisone or $\leq$ 0.45 mg/m^2/day dexamethasone]) is allowed. Topical steroids, inhaled steroids, and intrathecal steroids for CNS relapse prophylaxis are permitted.

The following medications are prohibited during the treatment and follow-up periods unless used as an anticancer agent after lack of adequate response to JCAR017:

- Donor lymphocyte infusion (DLI)
- Immunosuppressive therapies (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-TNF, anti-IL-6, or anti-IL-6R), unless needed for GVHD
- Non-protocol specified anticancer agents. Lymphocytic cytotoxic chemotherapy may be administered as an extraordinary measure to treat AEs of uncontrolled JCAR017 proliferation, CRS, or neurotoxicity unresponsive to other therapeutic interventions
- Cetuximab, or other anti-EGFR treatments, unless indicated for treatment of uncontrolled JCAR017 proliferation
- Experimental agents
- Radiation, unless needed for local control of a single tumor lesion

8.3. Concomitant Medications and Procedures

Lymphodepleting regimens accompany JCAR017 administration and utilize cyclophosphamide and fludarabine. Please refer to the currently approved cyclophosphamide and fludarabine phosphate Summary of Product Characteristics (Cyclophosphamide SmPC, 2014; Fludarabine SmPC, 2011).

To minimize the risk of infusion reactions, all subjects should be premedicated with paracetamol/acetaminophen 12.5 mg/kg (maximum dose 650 mg) PO (or IV at an equivalent dose) and diphenhydramine hydrochloride 1 mg/kg (maximum dose 50 mg) PO or IV 30 to 60 minutes prior to JCAR017 infusion (see Section 7.2.2). If diphenhydramine hydrochloride is not commercially available or a subject cannot tolerate diphenhydramine hydrochloride, premedication with an equivalent antihistamine may be substituted.

Supportive care for the management of CRS is detailed in Appendix F. In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as sCRS. Please refer to the currently approved Actemra®/ RoActemra® package inserts. As per the approved European Union (EU) SmPCs for CAR T therapy, the EMA is expecting a minimum of 4 doses of tocilizumab to be available prior to infusion for the management of CRS. However, as a JCAR017 Investigator, it is important to understand that the JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurotoxicity and the recommended use of tocilizumab is different from the CRS management algorithms of the approved CAR Ts. Hence, Celgene requires that all JCAR017 global sites (eg, US and EU) must have at least 2 doses of tocilizumab available prior to infusion per a given subject. It is recommended to resupply in case tocilizumab is given.

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

In some cases, steroids (eg, dexamethasone) may also be given for the treatment of CRS or NT.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 1/2 open-label, single-arm, multicohort study, to identify a safe and tolerable dose and to evaluate the safety and efficacy of JCAR017 in pediatric subjects with r/r B-ALL and B-NHL.

9.1.1. Phase 1

Up to 5 dose levels of JCAR017 will be evaluated (Table 6) in r/r B-ALL pediatric subjects. Dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm (Guo, 2017) as described in Section 3.1 until the RP2D has been identified. Based on the cumulative safety, PK and preliminary efficacy data, a RP2D will be selected in consultation with the SRC based on data from at least 10 pediatric subjects treated at the identified RP2D. Analysis of the JCAR017 manufactured product may also be considered.

9.1.2. Phase 2

In Phase 2, pediatric subjects (< 18 years of age) will enroll into one the following disease cohorts to further evaluate the efficacy and safety of JCAR017 at the identified RP2D in Phase 1.

- Cohort 1: r/r B-ALL
- Cohort 2: MRD+ B-ALL
- Cohort 3: r/r B-NHL (DLBCL, BL, or PMBCL)

Endpoints which are rate/proportion based shall show the number of subjects eligible for a given analysis along with the rate (percentage) and corresponding Clopper-Pearson 95% confidence interval (CI), while time-to event data shall be analyzed by Kaplan-Meier curves and the proportion of subjects remaining event free at given time points presented along with the median time. Greenwood 95% Cis shall be given. Descriptive statistics shall also be presented for time-to-event data such as number of subjects censored or having an event. Safety data will be presented by frequency according to the preferred term and system organ class they are categorized as. Efficacy based data will be analyzed by the non-selected dose levels from Phase 1 and by disease cohort (Phase 2 subjects and subjects treated at the RP2D in Phase 1) while safety data will be analyzed by the non-selected dose levels from Phase 1, disease cohort (Phase 2 subjects and subjects treated at the RP2D in Phase 1), and in aggregate across pediatric subjects receiving RP2D, and in aggregate of all pediatric subjects regardless of dose level.

All efficacy endpoints shall primarily be analyzed according to the central response assessment by IRC while the local response assessments shall form part of a select secondary/sensitivity analysis.

Full data analysis details will be outlined in the statistical analysis plan (SAP).

A risk-group sub-analysis with descriptive statistics and comparison between groups will be included as part of the overall analysis, provided a sufficient number of subjects are within certain risk-group categories; further detail will be provided in the SAP. The risk-groups to be analyzed, provided sufficient number of subjects are enrolled into the various sub-groups, are:

- Age at diagnosis
- Gender
- Race
- Prior response status (eg, primary refractory versus relapse to last prior therapy, prior HSCT, etc)
- Baseline CNS disease
- Timing of relapse
- Site of relapse
- Geography
- Stem cell transplant eligibility
- Baseline tumor burden and presence/absence of extramedullary disease
- Cytogenetics

Up to 20 additional subjects between 18 and 25 years of age may be enrolled in an optional cohort in Phase 2 and treated with JCAR017 at the RP2D. Subjects enrolled that are aged 18 to 25 years will not be considered for the primary endpoint of Phase 2. Efficacy and safety for subjects aged 18 to 25 years shall be fully reported alongside and in aggregate with subjects aged < 18 years of age.

9.2. Study Population Definitions

9.2.1. Informed Consent/Assent Population:

The Informed Consent/Assent Population includes all subjects for whom informed consent/assent was provided for this study.

9.2.2. Pre-treatment Population:

The Pre-treatment Population will consist of all subjects who are screened successfully into the study and either did or did not receive a JCAR017 infusion. The Pre-treatment Population shall be used for analysis of the JCAR017 manufacturing feasibility endpoint (where leukapheresis took place).

9.2.3. Dose-limiting Toxicity Analysis Population:

The DLT Analysis Population will include all Phase 1 enrolled subjects who received a JCAR017 infusion and completed 28 days post JCAR017 infusion, the DLT assessment period, if having not been observed as having a DLT before this point. The DLT Analysis Population will be used for identification of the RP2D as described in Section 3.1.

[redacted] In addition, pediatric subjects at DL1 who are retreated with JCAR017

intra-patient dose escalation in Phase 1 will not be included in the mTPI-2 algorithm to estimate DLT rates at DL2.

Relapsed/refractory B-ALL subjects who demonstrated morphological remission and are MRD+ or MRD negative upon restaging prior to initiation of lymphodepleting therapy will still be evaluable for the DLT Analysis Population in Phase 1 if they meet other analysis criteria.

9.2.4. Efficacy Analysis Population:

The Efficacy Analysis Population will include all subjects who fulfill all study eligibility criteria (prospectively and retrospectively) and receive JCAR017 infusion in accordance with drug product release specifications (ie, conforming JCAR017 product). [redacted] The Efficacy Analysis Population will be used for analysis of all efficacy-based endpoints. For the purpose of the primary endpoints, subjects ineligible for the Efficacy Analysis Population will be replaced.

Subjects who demonstrate morphological remission and are MRD negative upon restaging prior to initiation of lymphodepleting therapy (ie, no baseline disease) will be treated and followed on study but will not be considered evaluable for the Efficacy Analysis Population and may be replaced.

9.2.5. Safety Analysis Population:

The Safety Analysis Population will include all enrolled subjects who received a JCAR017 infusion. The Safety Analysis Population shall be used for analysis of the safety-based endpoints, and if different from the Efficacy Analysis Population, applied to the analysis of efficacy-based endpoints as a secondary analysis.

9.2.6. Pre-treatment Safety Analysis Population:

The Pre-treatment Safety Analysis Population will include all enrolled subjects who receive LD chemotherapy regardless of receiving a JCAR017 infusion or not. The Pre-treatment Safety Analysis Population shall be used for analysis of the safety data collected during the pre-treatment period.

[redacted]

9.2.8. Pharmacokinetic Analysis Population:

The PK Population will include all subjects who received JCAR017 infusion and have at least one measurable JCAR017 concentration. The evaluable subjects in the PK population will be included in the PK data analysis.

9.2.9. Patient Reported Outcome Analysis Population

The Patient Reported Outcome (PRO) analysis set will include all subjects who complete their baseline (screening or pre-treatment) questionnaires, have received JCAR017 and had at least one post-baseline PRO assessment.

9.3. Sample Size and Power Considerations

Assuming an 18% enrollment dropout rate (defined as subjects enrolled but not eligible for the primary endpoint analysis of the respective Phase of the study), a total of 124 subjects may be enrolled to ensure that approximately 101 primary endpoint evaluable subjects are treated with JCAR017.

Up to 20 additional B-ALL subjects between 18 and 25 years of age may also be enrolled in an optional cohort in Phase 2.

9.3.1. Phase 1

The Phase 1 portion of the study will utilize the mTPI-2 algorithm to help identify a RP2D in pediatric r/r B-ALL subjects.

The target DLT rate is set as 30%. Dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm (Guo, 2017) with a target DLT rate of 30% and an equivalence interval of 25% to 35%. A dose level will be considered unsafe, with no additional pediatric subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% ie, P (DLT > 30%|data) > 95% with at least 3 pediatric subjects treated at that dose level. Appendix G provides the decision table of mTPI-2 for each dose level. For a dose level to be shown safe per the mTPI-2 algorithm, at least 3 DLT-evaluable pediatric subjects must have completed the DLT period and the level estimated to be safe. The RP2D for pediatric subjects will be selected in consultation with the SRC based on data from at least 10 pediatric subjects treated at this dose level. The final number of subjects will depend on the number of dose levels tested and the number of DLTs observed within each cohort. Non-DLT-evaluable subjects will be replaced.

At least 11 DLT-evaluable pediatric (< 18 years of age) subjects will be treated in Phase 1. This is the minimum number of pediatric subjects to allow the study to continue to Phase 2. Up to 30 DLT-evaluable pediatric subjects will be included in Phase 1 to determine the RP2D assuming all dose levels enroll/treat the maximum number of subjects and no subjects are replaced.

9.3.2. Phase 2

The Phase 2 study population will consist of up to 71 evaluable pediatric subjects (< 18 years of age), should all cohorts below enroll the maximum number of subjects and assuming no subjects are replaced. The 10 or more pediatric subjects treated at the RP2D in Phase 1 will form part of the sample size (ie, Cohort 1 and Cohort 2), totaling at least 81 evaluable pediatric subjects in Phase 2.

Up to 20 subjects between 18 and 25 years of age may be enrolled in Phase 2 and will receive JCAR017 at the RP2D.

9.3.2.1. Cohort 1 (r/r B-ALL)

Assuming a 1-sided 5% significance level and 80%, along with the boundary to reject the null hypothesis or ORR = 75% vs. the boundary to accept the alternative hypothesis of ORR = 90%, a total of 48 evaluable subjects for the primary endpoint are required based on Simon's Optimal two-stage design (13 subjects in Stage 1 and a further 35 subjects in Stage 2). For the study treatment to be considered successful in this cohort, a total of 41 or more of the 48 subjects are required to have achieved a CR or CRi on Day 28, confirmed on Day 56. Subjects who enroll in Cohort 2 but demonstrate morphologic relapse upon restaging prior to initiation of lymphodepleting therapy will be included in Cohort 1.

9.3.2.2. Cohort 2 (MRD+ B-ALL)

Assuming a 1-sided 5% significance level and 80%, along with the boundary to reject the null hypothesis of MRD negative rate = 60% vs. the boundary to accept the alternative hypothesis of MRD negative rate = 85%, a total of 23 evaluable subjects for the primary endpoint are required based on Simon's Optimal two-stage design (9 subjects in Stage 1 and a further 14 subjects in Stage 2). For the study treatment to be considered successful in this cohort, a total of 18 or more of the 23 subjects are required to have a CR or CRi with an MRD negative BM on Day 28, confirmed on Day 56. Subjects that enroll in Phase 1 at the RP2D and Cohort 1 in Phase 2, who demonstrate morphological remission and are MRD+ upon restaging prior to initiation of lymphodepleting therapy will be included in Cohort 2.

9.3.2.3. Cohort 3 (B-NHL)

There is no formal sample size calculation; however, due to the low anticipated enrollment rate, the sample size of 10 pediatric subjects has been considered a feasible number that can be enrolled in order to gain preliminary efficacy data regarding the primary endpoint ORR, defined as the proportion of subjects achieving a CR or partial response (PR) on Day 28.

Should the required number of subjects achieving a response on Day 28 (Cohort 3), confirmed on Day 56 (Cohort 1) or MRD negative response on Day 28, confirmed on Day 56 (Cohort 2), be reached before the total required number of subjects for a given cohort can be enrolled, that given cohort may stop enrolment and declare the treatment positive in that given cohort with regard to the primary endpoint. Alternatively, if it is clear that the required number of primary endpoint responders will not be observed within the specified sample size for a given cohort then enrollment to that given cohort may be stopped due to lack of efficacy.

9.4. Background and Demographic Characteristics

The baseline characteristics of subjects will be summarized by dose level and cohort using the Safety Analysis Population. The age, weight, height, and other continuous demographic and baseline variables will be summarized using descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum). Lansky/Karnofsky performance status, gender, rate, and other categorical variables will be summarized with frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred terms or names, wherever applicable. All baseline characteristics and demographics will also be displayed in listings.

9.5. Subject Disposition

Subject disposition shall be presented by dose level and cohort for subjects in the Pre-treatment Safety Analysis Population and the Safety Analysis Population. For the pre-treatment period, treatment period and for the Post-Treatment Follow-up Period, the proportion of subjects entering, completing or discontinuing, along with the primary reason for discontinuation will be summarized using frequency and percentages. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations while protocol deviation and violations will be presented in a listing.

9.6. Efficacy Analysis

9.6.1. Phase 2 Primary Endpoints

9.6.1.1. Overall Response Rate

The primary endpoint of ORR will be analyzed for subjects in Cohort 1 and Cohort 3 subjects. Each cohort shall be analyzed separately. For each ORR calculated, the corresponding Clopper-Pearson 95% CI will be calculated.

Subjects without a Day 28 (Cohort 1 and Cohort 3) and/or Day 56 response assessment (Cohort 1) for whatever reason will be considered a non-responder with regard to the ORR.

Response assessment data collected after start of a new anticancer treatment or HSCT will not be considered for the ORR.

9.6.1.1.1. Cohort 1

Overall Response Rate is defined as the proportion of subjects achieving a confirmed CR or Cri on Day 28, confirmed on Day 56, divided by the number of subjects included in the analysis.

The first disease assessment will be performed at 28 days after JCAR017 infusion however if the subject cannot be assessed for CR/CRi due to hypoplastic marrow, a repeat marrow examination should be performed when there is evidence of hematopoietic recovery so that remission can be assessed for the first time.

Therefore, 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, BM, CSF and extramedullary disease assessment (where applicable) confirmed at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. If additional assessments are performed in the same evaluation, they will also need to show remission status.

9.6.1.1.2. Cohort 3

Overall Response Rate is defined as the proportion of pediatric B-NHL subjects achieving a CR or PR on Day 28 divided by the number of subjects included in the analysis.

9.6.1.2. MRD Negative Rate

The primary endpoint of MRD negative rate will be analyzed for subjects in Cohort 2 only.

The MRD negative rate is defined as the proportion of subjects achieving a CR or CRi with an MRD negative BM on Day 28, confirmed on Day 56, divided by the number of subjects included in the analysis.

The first disease assessment will be performed at 28 days after JCAR017 infusion however if the subject cannot be assessed for CR/CRi due to hypoplastic marrow, a repeat marrow examination should be performed when there is evidence of hematopoietic recovery so that MRD negative remission can be assessed for the first time.

Therefore, in order for the best overall disease response to be categorized as MRD negative CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood, BM, CSF and extramedullary disease assessment (where applicable) with no MRD detected in BM (below the level of detection [<0.01%] by validated assay at a central analytical laboratory), confirmed at a minimum of 4 weeks (28 days) after the initial achievement of MRD negative CR or CRi. If additional assessments are performed in the same evaluation, they will also need to show remission status.

For each MRD negative rate calculated, the corresponding Clopper-Pearson 95% CI will be calculated.

Subjects with an unknown MRD status must be included in the analysis as MRD positive.

Response assessment data collected after start of a new anticancer treatment or HSCT will not be considered for the MRD negative rate.

9.6.2. Phase 1 and Phase 2 Secondary Endpoints

9.6.2.1. Overall Response Rate

The ORR will be analyzed for each of the non-selected dose levels in Phase 1. Each cohort shall be analyzed separately. For each ORR calculated, the corresponding Clopper-Pearson 95% CI will be calculated. Subjects without a Day 28 and/or Day 56 response assessment for whatever reason will be considered a non-responder with regard to the ORR.

Response assessment data collected after start of a new anticancer treatment or HSCT will not be considered for the ORR.

9.6.2.2. MRD Negative Response Rate

For B-ALL subjects only, the secondary objective of MRD response rate will be analyzed for the non-selected dose levels in Phase 1 and Cohort 1 in Phase 2.

The MRD Response Rate is defined as the proportion of subjects achieving a confirmed CR or CRi with no MRD detected in BM (below the level of detection [<0.01%] tumor cells by a validated assay), up to 24 months after JCAR017 infusion over the number of subjects available for the analysis.

For each Response Rate calculated, the corresponding Clopper-Pearson 95% CI will be calculated.

Response assessment data collected after start of a new anticancer treatment or HSCT will not be considered for the Response Rate.

9.6.2.3. Duration of Response

Duration of response is defined as the time from first observed response until either disease progression, or relapsed disease, or death. Only subjects observed with a response shall be included in the analysis of DOR. The median DOR time and the proportion of subjects remaining with a response at 6, 12, 24 months, and at close of study along with the corresponding Greenwood 95% CI will be calculated using Kaplan-Meier methods. Subjects who are alive and remain in disease response at the time of analysis will be censored at the time of their last adequate disease assessment or at the time of starting a new anticancer therapy, whichever is first. Due to the low number of subjects to be included in the analysis, additional summary statistics will be presented. Each cohort shall be analyzed separately. Subjects who demonstrate morphological remission and are MRD negative upon restaging prior to initiation of lymphodepleting therapy (ie, no baseline disease) will also be considered for DOR (ie, time to relapse).

9.6.2.4. Relapse-free Survival

Relapse-free survival (RFS) is defined as the time from JCAR017 infusion until disease progression or disease relapse or death of any cause, whichever occurs first. The median RFS time and proportion of subjects remaining relapse-free at 6, 12, 24 months, and at close of study as well as the median of subjects within a cohort having an RFS even, along with the corresponding Greenwood 95% CI will be calculated using Kaplan-Meier methods. Subjects remaining relapse-free at the time of analysis will be censored at the time of their last adequate disease assessment. Additionally, subjects will be censored at the time of starting a new anticancer therapy if having not had disease progression or disease relapse previously. Due to the low number of subjects to be included in the analysis, additional summary statistics will be presented. Each cohort shall be analyzed separately.

9.6.2.5. Event-free Survival

Event-free survival is defined as the time from JCAR017 infusion until either disease progression or disease relapse, start of a new anticancer therapy or death of any cause, whichever occurs first. The median EFS time and proportion of subjects remaining event-free at 6, 12, 24 months, and at close of study as well as the median of subjects within a cohort having an EFS even, along with the corresponding Greenwood 95% CI will be calculated using Kaplan-Meier methods. Subjects remaining event-free at the time of analysis will be censored at the time of their last adequate disease assessment. Due to the low number of subjects to be included in the analysis, additional summary statistics will be presented. Each cohort shall be analyzed separately.

9.6.2.6. Overall Survival

Overall survival is defined as the time from JCAR017 infusion until death of any cause. The median OS time and proportion of subjects remaining alive at 6, 12, 24 months, and at close of study, along with the corresponding Greenwood 95% CI, calculated using Kaplan-Meier methods will be presented. Subjects remaining alive at the time of analysis will be censored at the time they were last known to be alive. Due to the low number of subjects to be included in the analysis, additional summary statistics will be presented. Each cohort shall be analyzed separately.

9.6.2.7. Hematopoietic Stem-cell Transplant Rate

The HSCT rate is defined as the proportion of subjects who undergo HSCT after receiving a JCAR017 infusion and achieving a response divided by the number of subjects available for the analysis. The time of proceeding to HSCT is defined as the time of commencing the conditioning regimen as required for HSCT.

For each HSCT rate calculated, the corresponding Clopper-Pearson 95% CI will be calculated.

Each cohort shall be analyzed separately.

9.6.2.8. Best Overall Response Rate

Best overall response (BOR) rate is defined as the percentage of B-NHL subjects achieving a BOR (either CR or PR) following JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy, or HSCT.

Subjects with an unknown or missing response will be included in the analysis counted as non-responder.

9.7. Safety Analysis

9.7.1. Phase 1 Primary Endpoint

9.7.1.1. Recommended Phase 2 Dose

The Phase 1 portion of the study will utilize the mTPI-2 algorithm to help identify a safe and tolerable dose (RP2D) in pediatric subjects as described in Section 9.3.1.

Based on the cumulative safety, PK and preliminary efficacy data, a RP2D will be selected in consultation with the SRC based on data from at least 10 pediatric subjects treated at the RP2D. Analysis of the JCAR017 manufactured product may also be considered.

9.7.2. Phase 1 and Phase 2 Secondary Endpoints

9.7.2.1. Adverse Events

Adverse Events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (latest version). This study will utilize the NCI CTCAE (version 4.03 or greater) for toxicity grading and performance reporting. All AE data shall be presented by cohort and in aggregate.

Treatment-emergent adverse events are defined as any AE occurring or worsening on the day of the JCAR017 infusion until 90 days post-treatment (JCAR017 infusion). All treatment-emergent adverse events (TEAEs), AEs related to the study treatment, SAEs, and AEs leading to death will be summarized as by subject (worse recorded grade) per event type (organ class and preferred term) and grade. A summary of AEs with NCI CTCAE (version 4.03 or greater) Grade 3 or higher, as well as the most frequent preferred terms, will also be provided by grade and term.

Cross tabulations will be provided to summarize frequencies of abnormalities.

By-subject listings will be provided for all relevant safety data. Graphical displays and figures will be provided where useful to assist in the interpretation of results.

9.7.2.2. Deaths

Deaths occurring up to 90 days after the JCAR017 infusion, and during the Post-Treatment Follow-up ’Period shall be summarized by frequency of occurrence and corresponding percentage by primary cause of death per cohort and in aggregate.

9.7.2.3. Clinical Laboratories

Clinical laboratory values will be graded according to NCI CTCAE (version 4.03 or greater) for applicable tests. Baseline grade and worst grade during treatment for selected laboratory results will be summarized. Shift from baseline to the worst grade observed during the treatment for selected laboratory results will also be provided. All laboratory data shall be presented by cohort and in aggregate.

9.7.2.4. Vital Signs

For vital signs, shift from baseline to worst during the treatment in below, within, and above the normal ranges will be displayed in cross-tabulations. Summary statistics (N, mean, standard deviation, median, minimum, and maximum) of observed and change from baseline values will be presented. All vital signs data shall be presented by cohort and in aggregate.

9.8. Interim Analysis

One interim analysis is planned for Cohort 1 and one for Cohort 2. Interim analyses will be based on cleaned efficacy data relating to the primary endpoint and will use the Efficacy Analysis Populations using centrally reviewed response assessment data.

In Cohort 1, the interim analysis will be conducted once primary endpoint related efficacy data from the first 13 subjects eligible for the primary endpoint is available, ie, up to Day 56 post infusion if having a CR or CRi at Day 28, or Day 28 if not having a CR or CRi at that time, and earlier still if the subject has a disease progression, disease relapse or discontinues from the study prior to Day 28. If the number of subjects observed as having a CR or CRi at Day 28, confirmed at Day 56, is 11 or more, then enrollment into Stage 2 will continue as planned; otherwise the cohort will be closed to further enrollment and the study treatment in this cohort concluded as unpromising. Enrollment will be suspended while assessing Stage 1 for the Stage 2 go/no-go decision; if it is clear before reaching the 13th subject that the criteria to move into Stage 2 has been met, then enrollment will not be suspended. If it is clear before enrollment of the 13th subject that the required number of confirmed responses for going into Stage 2 will not be met, the cohort will close to enrollment due to futility prior to enrolling the entire 13 subjects.

In Cohort 2, the interim analysis will be conducted once primary endpoint related efficacy data from the first 9 subjects eligible for the primary endpoint is available, ie, up to Day 56 post infusion if having a MRD negative response at Day 28, or Day 28 if not having a MRD negative response at that time, and earlier still if the subject has a disease progression or discontinues from the study prior to Day 28. If the number of subjects observed as having a MRD negative response at Day 28, confirmed at Day 56, is 7 or more, then enrollment into Stage 2 will continue as planned; otherwise the cohort will be closed to further enrollment and the study treatment in this cohort concluded unpromising. Enrollment will be suspended while assessing Stage 1 for the Stage 2 go/no-go decision; if it is clear before reaching the ninth subject that the criteria to move into Stage 2 has been met, then enrollment will not be suspended. If it is clear

before enrollment of the ninth subject that the required number of confirmed responses for going into Stage 2 will not be met, the cohort will close to enrollment due to futility prior to enrolling the entire 9 subjects.

Interim analyses and conclusions will be performed by Celgene and confirmed by the DSMB and/or the SSC.

9.9. Other Topics

9.9.1. JCAR017 Manufacturing Feasibility

Evaluation of the feasibility of manufacturing JCAR017 will be measured by the percentage of product generated successfully. Specifically, this feasibility endpoint will be conducted on the first 10 pediatric subjects enrolled, regardless of dose; should product generation be successful for < 70% (< 7/10) of the subjects, the study will be temporarily suspended pending review by Celgene/DSMB. Analysis of this endpoint will be based upon the Pre-treatment Population.

Feasibility endpoint:

The number and percentage of subjects who are eligible for study treatment but not able to successfully generate a JCAR017 cell product, along with the reason(s) for manufacturing failure, will be summarized.

Successful product will be defined as:

- JCAR017 product was generated and able to be QC released [redacted] for infusion.

Unsuccessful product is defined as:

- No JCAR017 product could be generated after two manufacturing attempts using a single apheresis product for starting material or
- Product was unable to be QC released for infusion

9.9.2. Safety Review Committee (SRC)

During Phase 1, the SRC will be convened to review DLTs and to recommend a Phase 2 dose based on an integrated assessment of the safety, PK data and preliminary efficacy information.

This committee will be composed of the medical monitor, drug safety physician, and statistician as well as up to 5 active Investigators. Operational details for the SRC will be detailed in a separate SRC charter.

9.9.3. Data Safety Monitoring Board (DSMB)

An independent data safety monitoring board (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 selected 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 twice a year throughout the trial and as needed to address any safety issues that may arise. Subject safety will be evaluated as specified in DSMB charter. The DSMB will provide advice to Celgene as outlined in the DSMB charter. The effectiveness of the risk mitigation plan will be reviewed by the DSMB at each meeting. Operational details for the DSMB will be detailed in the DSMB charter.

9.9.4. Scientific Steering Committee (SSC)

The conduct of this trial will be overseen by a Scientific Steering Committee (SSC), comprised of Investigators that may or may not be participating in the study. The SSC will serve in an advisory capacity to Celgene. Operational details for the SSC will be detailed in a separate SSC charter.

Note: The SSC is separate from the DSMB.

9.9.5. Exploratory Analysis

The PK, [redacted] and the health utilization analyses will be specified in separate analysis plans. The exploratory endpoints of the study are listed in Section 2; details of the exploratory analyses are provided in the statistical analysis plan.

Planned exploratory analyses will include:

- Best response and ORR by sub-group/risk-group
- Prior HSCT impact on response
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Safety: The effect of treatments directed at sCRS and neurotoxicity on duration and severity of sCRS and neurotoxicity
- [redacted]
- Hospital resource utilization: Number of inpatient days, ICU days, and outpatient visits
- Patient reported outcomes

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. (See Section 7.2.7 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and, on the AE, eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for JCAR017, fludarabine or cyclophosphamide overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

Adverse events must be recorded as shown in Table 8. If they meet the seriousness criteria, they will be reported to Drug Safety as provided in Section 10.5.

Table 8: Reporting Periods for Adverse Events

Start	End	Required Reporting
Signing of informed consent	Start of LD chemotherapy	Only AEs related to any study procedure
Start of LD chemotherapy	Day 90, after JCAR017 infusion	All AEs, irrespective of causality, and any toxicity change to ongoing AEs will be recorded in the eCRF as a separate AE record
Day 91, after JCAR017 infusion	End of study	Only AEs related to any study procedure or JCAR017 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

AEs = adverse events; eCRF = electronic case report form; LD = lymphodepleting.

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

made known to the Investigator at any time thereafter that are suspected of being related to IP will be recorded as well. Documentation must be supported by an entry in the subject's source document.

A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome. In addition to recording CRS and neurotoxicity as a diagnosis, the signs and symptoms of CRS and neurotoxicity will be recorded on separate eCRFs. Any medical condition already present prior to first LD chemotherapy should not be reported as an AE unless the medical condition is related to any study procedure and increases in severity. In this case, it should be reported as an AE and indicated as a worsening event.

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 (eg, 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 eCRF for detailing specific adverse events of special interest (AESI; ie, signs and symptoms of CRS and neurotoxicity), will be utilized for the purpose of adequately describing the expected risks of JCAR017 and the recommendations for managing these risks.

Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs meeting the criteria described in Table 8 must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is defined as any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

  Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Any confirmed detectable result from [redacted] testing, as well as any observation of clonal outgrowth (clonal dominance), or monoclonality, as a result of the integrated vector will be reported as an SAE within 24 hours.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, BM sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the LD chemotherapy and/or JCAR017, action taken regarding LD chemotherapy and/or JCAR017, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03 or greater);

Note: Cytokine release syndrome will be graded as per Table 10.

Adverse events that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of LD chemotherapy and JCAR017 and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to LD chemotherapy or JCAR017 administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of LD chemotherapy or JCAR017 caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the LD chemotherapy or JCAR017 and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional LD chemotherapy that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with investigational products as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of investigational products, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

Serious adverse events will be followed until they return to baseline, the event stabilizes or is no longer considered clinically significant by the Investigator; the subject dies or withdraws consent; or study closure.

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study;
- Requires treatment, modification/interruption of LD chemotherapy or JCAR017 cell product dose, or any other therapeutic intervention (including transfusions or growth factors); or
- Is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test) occurring at any time after receipt of lymphodepleting chemotherapy or infusion of JCAR017 in either a FCCBP/FCBP or partner of childbearing potential of a male subject are immediately reportable events. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

10.4.1. Female Children of Childbearing Potential/Females of Childbearing Potential

The Investigator will follow the female subject until completion of the pregnancy and afterwards up to 1 year of the newborn baby, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to LD chemotherapy or JCAR017 should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours after the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject taking LD chemotherapy and/or JCAR017 becomes pregnant, the male subject should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The pregnant partner will be asked for consent (if permitted by local regulations) for follow-up by the Investigator until completion of the pregnancy and afterwards up to 1 year of the newborn baby.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to LD chemotherapy or JCAR017) recorded in the eCRF as described in Section 10.1.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Progressive disease is considered as a study endpoint and will not be reported as an SAE. However, any sign, symptom, or manifestation of progressive disease that meet any of the seriousness criteria will be reported as individual SAE.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant

initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.5.2. Death Reports

Deaths due to progressive disease will not be reported as an SAE unless considered related to LD chemotherapy or JCAR017 (ie, if assessed as lack of efficacy by the Investigator). Any sign, symptom, or manifestation of progressive disease that meet any of the seriousness criteria and result in death will be reported as individual SAEs. Any other AEs leading to death should be reported as an SAE according to Table 8.

10.6. Potential Risks and Management of Treatment Toxicities

A summary of potential risks and management of treatment toxicity is provided below for the IP. See the IB for a complete discussion of potential risks associated with JCAR017.

10.6.1. Management of Toxicities Associated with JCAR017

Cytokine release syndrome (CRS) and neurologic toxicities (NT) are associated with CAR T cell therapies. Celgene has developed specific toxicity management guidelines (TMG) for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs (Appendix F). These recommendations are based on the CRS revised grading system (Lee, 2014) and the Common Toxicity Criteria for Adverse Events (CTCAE) and need to be used for grading of CRS and NT to guide management in this trial.

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

10.6.1.1. Cytokine Release Syndrome

Administration of JCAR017 is associated with cytokine release syndrome (CRS). Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (Lee, 2014), and management can be complicated by concurrent conditions. With JCAR017, CRS usually occurs within two weeks after infusion (Abramson, 2017).

- Fever, especially high fever (≥ 38.5°C or ≥ 101.3°F), is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.

- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurological toxicity has been observed concurrently with CRS.
- With other CAR T cell products, CRS has been reported in a few cases to be associated with findings of macrophage activation syndrome/hemophagocytoic lymphohistiocytosis (MAS/HLH), and the physiology of the syndromes may overlap.

Please refer to Appendix F for detailed description of CRS, grading and treatment recommendations. Note: Cytokine release syndrome will be graded as per Table 10.

10.6.1.2. Fever

The possibility of CRS should be considered for all subjects with fever (≥ 38°C or ≥ 100.4°F) following JCAR017 treatment. Subjects should be monitored closely for hemodynamic instability and changing neurologic status. Febrile subjects, neutropenic or otherwise, should be evaluated promptly for infection and managed per institutional or standard clinical practice.

10.6.1.3. Cytopenias

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

10.6.1.4. Infections

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

10.6.1.5. Neurologic Toxicities

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

Please refer Appendix F for detailed description of neurologic toxicities, grading and treatment recommendations.

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

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

10.6.1.7. Infusion Reactions

Administration of JCAR017 may cause infusion reactions, such as fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea.

To minimize the risk of infusion reactions, all subjects should be pre-medicated with acetaminophen and diphenhydramine (see Section 7.2.2). Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and antiemetics. Corticosteroids should be avoided because of the potential impact on efficacy of infused JCAR017 cells. Rigors may be treated with meperidine.

The following guidelines should be followed for infusion reactions:

- Grade 1: administer symptomatic treatment; continue JCAR017 administration of both CD8+CAR+ and CD4+CAR+ components at the same dose and rate
- Grade 2: stop administration of JCAR017; administer symptomatic treatment, and resume JCAR017 administration of both CD8+CAR+ and CD4+CAR+ components at a reduced rate of administration only after symptoms resolution
- Grade 3: stop administration of JCAR017, administer symptomatic treatment, and resume at a reduced rate of administration only after symptoms resolve. If Grade 3 reaction recurs, discontinue JCAR017 administration; no further CD8+CAR+ or CD4+CAR+ components of JCAR017 should be administered
- Grade 4: discontinue administration of JCAR017 and administer symptomatic treatment as necessary; no further no further CD8+CAR+ or CD4+CAR+ components of JCAR017 should be administered

10.6.1.8. Tumor Lysis Syndrome

Both LD chemotherapy employed in this protocol and JCAR017 have caused TLS in adult B-NHL subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia; see

Appendix E), and subjects at high risk for developing TLS, such as those with high disease burden and high cell turnover, should receive prophylactic treatment, including administration of allopurinol and hydration, per standard clinical practice.

[redacted]

10.6.1.10. Graft-Versus-Host Disease

The likelihood of GVHD occurring with CAR T cell therapy is low, but it remains a theoretical risk. Subjects who have undergone allogeneic HSCT and who have active, acute or chronic GVHD at screening are excluded from enrolling in this protocol. However, due to residual donor engraftment, some or all T cells of JCAR017 may be of donor origin. Subjects who received a previous allogeneic HSCT will be assessed for donor chimerism at screening and will be monitored closely throughout the study for signs of GVHD.

10.6.1.11. Uncontrolled T Cell Proliferation

JCAR017 could theoretically proliferate out of control. If uncontrolled JCAR017 proliferation occurs, subjects may be treated with high-dose steroids (eg, methylprednisolone 1 to 3 g/kg/day, tapered over 7 days) or LD doses of cyclophosphamide (1 to 3 g/m^2 IV). If an Investigator suspects uncontrolled JCAR017 proliferation, Celgene should be contacted immediately. In an animal model the EGFR antibody cetuximab was used to ablate EGFRt-expressing CAR T cells in vivo (Wang, 2011). Currently, there is no data available on efficacy of cetuximab or other EGFR-directed antibodies for depletion of JCAR017 CAR T cells in humans.

[redacted]

[redacted]

10.6.1.13. Risks Associated with Lymphodepleting Chemotherapy

Subjects receiving JCAR017 will receive fludarabine and cyclophosphamide prior to treatment with JCAR017 to facilitate lymphodepletion and CAR T cell engraftment. Refer to the package inserts or summary of product characteristics for specific details surrounding the risks of fludarabine phosphate and cyclophosphamide.

10.6.1.14. Second Primary Malignancies

Second primary malignancies must be reported as SAEs. This includes any second primary malignancy, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICF until study end. These events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, x-rays, CT scans, etc.).

10.7. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to JCAR017 based on the Investigator's Brochure.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on Ips for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of JCAR017 in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC (see Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

10.8. Adverse Event of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the Investigator to Celgene. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Adverse events of special interest for JCAR017 include but are not limited to:

- Infusion reaction;
- Cytokine release syndrome (CRS);
- Neurological toxicity (NT);
- Macrophage activation syndrome (MAS);
- Tumor lysis syndrome (TLS)
- Infections
- Prolonged cytopenias
- Hypogammaglobulinemia

Further information regarding the list of AESI can be found in the statistical analysis plan (SAP).

11. DISCONTINUATIONS

11.1. Pre-treatment Period Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the Pre-treatment Period who undergoes leukapheresis but does not receive study treatment:

- Adverse Event
- Withdrawal of consent by subject/guardian
- Failure to meet treatment criteria
- Study drug manufacturing failure
- Death
- Physician decision
- Other (to be specified on the eCRF)

11.2. Treatment Period Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the Treatment Period:

- Adverse Event
- Withdrawal of consent by subject/guardian
- Death
- Lost to follow-up
- Physician decision
- Other (to be specified on the eCRF)

The reason for discontinuation should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by Celgene. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.3. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Withdrawal of consent by subject/guardian
- Death

- Lost to follow-up
- Unsuccessful manufacturing of JCAR017
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, the IP will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local regulations of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF/IAF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent/Assent

The Investigator must obtain informed consent/assent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent/assent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF/IAF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent/assent, the ICF/IAF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF/IAF. The revised ICF/IAF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local regulations.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF/IAF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF/IAF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF/IAF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of eCRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, IP storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/Ecs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA]) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. Product Quality Complaints may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging

damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted] or by contacting the Celgene Customer Care Center [redacted].

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

17. REFERENCES

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

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

Adusumilli PS, Cherkassky L, Villena-Vargas J, Colovos C, Servais E, Plotkin J, et al. Regional delivery of mesothelin-targeted CAR T cell therapy generates potent and long-lasting CD4-dependent tumor immunity. Sci Transl Med. 2014 Nov 05;6(261):261ra151.

Bleakley M, Shaw PJ, Nielsen JD. Allogeneic bone marrow transplantation for childhood relapsed acute lymphoblastic leukemia: comparison of outcome in patients with and without a matched family donor. Bone Marrow Transplant. 2002 Jul;30(1):1-7.

[redacted]

Borowitz MJ, Wood BL, Devidas M, Loh ML, Raetz EA, Salzer WL, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. Blood. 2015 Aug 20;126(8):964-71.

Bos R, Sherman LA. CD4+ T-cell help in the tumor milieu is required for recruitment and cytolytic function of CD8+ T lymphocytes. Cancer Res. 2010 Nov 01;70(21):8368-77.

Brentjens RJ, Riviere I, Park JH, Davila ML, Wang X, Stefanski J, 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 Nov 03;118(18):4817-28.

Burkhardt B, Waxman I. Adolescent Non-Hodgkin Lymphoma. 2012:329-47.

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004 Oct;127(1):3-11.

Cairo MS, Pinkerton R. Childhood, adolescent and young adult non-Hodgkin lymphoma: state of the science. British journal of haematology. 2016 May;173(4):507-30.

Chao MP. Treatment challenges in the management of relapsed or refractory non-Hodgkin's lymphoma - novel and emerging therapies. Cancer Manag Res. 2013;5(1):251-69.

[redacted]

Davila ML, Brentjens R, Wang X, Riviere I, Sadelain M. How do CARs work?: Early insights from recent clinical studies targeting CD19. Oncoimmunology. 2012 Dec 01;1(9):1577-83.

Dunleavy K, Steidl C. Emerging biological insights and novel treatment strategies in primary mediastinal large B-cell lymphoma. Seminars in hematology. 2015 Apr;52(2):119-25.

Eckert C, Flohr T, Koehler R, Hagedorn N, Moericke A, Stanulla M, et al. Very early/early relapses of acute lymphoblastic leukemia show unexpected changes of clonal markers and high heterogeneity in response to initial and relapse treatment. Leukemia. 2011 Aug;25(8):1305-13.

European Medicines Agency. Guideline on follow-up of subjects administered with gene therapy medicinal products. European Medicines Agency [Internet]. 2009 Oct 22. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001375.jsp&mid=WC0b01ac058002958d.

Faderl S, O'Brien S, Pui CH, Stock W, Wetzler M, Hoelzer D, et al. Adult acute lymphoblastic leukemia: concepts and strategies. Cancer. 2010 Mar 01;116(5):1165-76.

Food and Drug Administration. Briefing Document — Testing for replication competent retrovirus (RCR)/lentivirus (RCL) in retroviral and lentiviral vector based gene therapy products — Revisiting current FDA recommendations. Food and Drug Administration. 2010. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM232592.pdf.

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. Food and Drug Administration [Internet]. Food and Drug Administration. 2006 Oct. Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072961.htm.

Freyer DR, Devidas M, La M, Carroll WL, Gaynon PS, Hunger SP, et al. Postrelapse survival in childhood acute lymphoblastic leukemia is independent of initial treatment intensity: a report from the Children's Oncology Group. Blood. 2011 Mar 17;117(11):3010-5.

Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017 Jun 22;129(25):3322-31.

Gardner RA, Finney O, Smithers H, Leger K, Annesley CE, Summers C, et al. CD19 CAR T cell products of defined CD4:CD8 composition and transgene expression show prolonged functional persistence and durable MRD-negative remission in Pediatric and Young Adult B-cell ALL. Blood. 2016 128(22), 219.

Gaynon P, Schrappe M. Hematological Malignancies in Children, Adolescents and Young Adults. World Scientific Publishing Co., Inc.; 2012. Book Chapter 11, Childhood ALL; p. 197-224.

Gerrard M, Cairo MS, Weston C, Auperin A, Pinkerton R, Lambilliote A, et al. Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: results of the FAB/LMB 96 international study. British journal of haematology. 2008 Jun;141(6):840-7.

Gokbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012 Aug 30;120(9):1868-76.

[redacted]

Guo W, Wang SJ, Yang S, et al. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemp Clin Trials 2017;58:23-33.

[redacted]

Hochberg J, El-Mallawany NK, Abla O. Adolescent and young adult non-Hodgkin lymphoma. British journal of haematology. 2016 May;173(4):637-50.

James SE, Orgun NN, Tedder TF, Shlomchik MJ, Jensen MC, Lin Y, et al. Antibody-mediated B-cell depletion before adoptive immunotherapy with T cells expressing CD20-specific chimeric T-cell receptors facilitates eradication of leukemia in immunocompetent mice. Blood. 2009 Dec 24;114(27):5454-63.

Jourdain A, Auperin A, Minard-Colin V, Aladjidi N, Zsiros J, Coze C, et al. Outcome of and prognostic factors for relapse in children and adolescents with mature B-cell lymphoma and leukemia treated in three consecutive prospective "Lymphomes Malins B" protocols. A Societe Francaise des Cancers de l'Enfant study. Haematologica. 2015 Jun;100(6):810-7.

[redacted]

[redacted]

Kochenderfer JN, Yu Z, Frasheri D, Restifo NP, Rosenberg SA. Adoptive transfer of syngeneic T cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells. Blood. 2010 Nov 11;116(19):3875-86.

[redacted]

LeBien TW, Tedder TF. B lymphocytes: how they develop and function. Blood. 2008 Sep 01;112(5):1570-80.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-195. Erratum in: Blood. 2015;126(8):1048.

[redacted]

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019, Apr;25(4):625-38.

Li YS, Hayakawa K, Hardy RR. The regulated expression of B lineage associated genes during B cell differentiation in bone marrow and fetal liver. The Journal of experimental medicine. 1993 Sep 01;178(3):951-60.

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

[redacted]

Makita S, Yoshimura K, Tobinai K. Clinical development of anti-CD19 chimeric antigen receptor T-cell therapy for B-cell non-Hodgkin lymphoma. Cancer science. 2017 Jun;108(6):1109-18.

Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969; 44:291-303.

Marshall WA, Tanner JM (1970) Variations in pattern of pubertal changes in boys. Arch Dis Child. 1970 45:13-23.

[redacted]

Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018 Feb 1;378(5):439-48.

Minard-Colin V, Brugieres L, Reiter A, Cairo MS, Gross TG, Woessmann W, et al. Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead. Journal of clinical oncology. 2015 Sep 20;33(27):2963-74.

Molyneux EM, Rochford R, Griffin B, Newton R, Jackson G, Menon G, et al. Burkitt's lymphoma. Lancet (London, England). 2012 Mar 31;379(9822):1234-44.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Pediatric Acute Lymphoblastic Leukemia; V.1.2020 - May 2019. Available from: https://www.nccn.org.

Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. N Engl J Med. 2018 Feb 1;378(5):449-59.

Pegram HJ, Lee JC, Hayman EG, Imperato GH, Tedder TF, Sadelain M, et al. Tumor-targeted T cells modified to secrete IL-12 eradicate systemic tumors without need for prior conditioning. Blood. 2012 May 03;119(18):4133-41.

Pinkerton R, Cairo MS. Hematological Malignancies in Children, Adolescents and Young Adults. Singapore: World Scientific Publishing Company; 2012. Chapter 16, Childhood Non-Hodgkin Lymphoma; p. 299-328.

Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, et al. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. J Clin Oncol. 2015 Sep 20;33(27):2938-48.

Rabin KR, Gramatges MM, Margolin JF, Poplack DG. Principles and Practice of Pediatric Oncology. 7th ed. Philadelphia, PA: Wolters Kluwer Health; 2016. Chapter 19, Acute lymphoblastic leukemia; p. 463-97.

RoActemra® [Summary of Product Characteristics]. Welwyn Garden City, United Kingdom: Roche Products Limited. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf.

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

Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. Journal of Clinical Oncology. 2015;33(18):2106-2111. doi:10.1200/JCO.2014.59.0745.

Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010 Nov 11;116(19):3724-34.

[redacted]

Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. Annu Rev Med. 2015;66:145-59.

Schwartz GJ, Haycock GB, Edelmann CM, Jr., Spitzer AD. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976 Aug;58(2):259-63.

Seidemann K, Tiemann M, Lauterbach I, Mann G, Simonitsch I, Stankewitz K, et al. Primary mediastinal large B-cell lymphoma with sclerosis in pediatric and adolescent patients: treatment and results from three therapeutic studies of the Berlin-Frankfurt-Munster Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003 May 01;21(9):1782-9.

Shank BR, Do B, Sevin A, Chen SE, Neelapu SS, Horowitz SB. Chimeric Antigen Receptor T Cells in Hematologic Malignancies. Pharmacotherapy. 2017 Mar;37(3):334-45.

[redacted]

Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017 Jan;67(1):7-30.

[redacted]

Stamenkovic I, Seed B. CD19, the earliest differentiation antigen of the B cell lineage, bears three extracellular immunoglobulin-like domains and an Epstein-Barr virus-related cytoplasmic tail. The Journal of experimental medicine. 1988 Sep 1;168(3):1205-10.

Stiller CA, Desandes E, Danon SE, Izarzugaza I, Ratiu A, Vassileva-Valerianova Z, et al. Cancer incidence and survival in European adolescents (1978-1997). Report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006 Sep;42(13):2006-18.

Tasian SK, Loh ML, Hunger SP. Childhood acute lymphoblastic leukemia: Integrating genomics into therapy. Cancer. 2015 Oct 15;121(20):3577-90.

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

[redacted]

Toes RE, Ossendorp F, Offringa R, Melief CJCONJEMM, Pmid. CD4 T cells and their role in antitumor immune responses. The Journal of experimental medicine. 1999 Mar 01;189(5):753-6.

[redacted]

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

Vardiman JW. The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues: an overview with emphasis on the myeloid neoplasms. Chem Biol Interact. 2010 Mar 19;184(1-2):16-20.

Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009 Jul 30;114(5):937-51.

Vitolo U, Seymour JF, Martelli M, Illerhaus G, Illidge T, Zucca E, et al. Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2016 Sep;27(suppl 5):v91-v102.

[redacted]

Wang X, Chang WC, Wong CW, Colcher D, Sherman M, Ostberg JR, et al. A transgene-encoded cell surface polypeptide for selection, in vivo tracking, and ablation of engineered cells. Blood. 2011 Aug 4;118(5):1255-63.

18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
[redacted]	
B-ALL	B-cell acute lymphoblastic leukemia
B-NHL	B-cell non-Hodgkin lymphoma
BCA	B-cell aplasia
β-hCG	Beta human chorionic gonadotropin
BFM	Berlin-Frankfurt-Münster
BL	Burkitt lymphoma
BM	Bone marrow
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BOR	Best overall response
CAR	Chimeric antigen receptor
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete response
eCRF	Electronic case report form
CRi	CR with incomplete blood count recovery
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ddPCR	Droplet digital polymerase chain reaction
DFS	Disease-free survival
DL	Dose level

Abbreviation or Specialist Term	Explanation
DLBCL	Diffuse large B-cell lymphoma
DLI	Donor lymphocyte infusions
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMB	Data Safety Monitoring Board
DVT	Deep venous thrombosis
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
EEA	European Economic Area
EEG	Electroencephalogram
EFS	Event-free survival
EGFRt	Truncated human epidermal growth factor receptor
EMA	European Medicines Agency
EOS	End of study
EU	European Union
FCBP	Female of childbearing potential
FCCBP	Female children of childbearing potential
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GVHD	Graft-versus-host disease
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLA-DR	Human leukocyte antigen – antigen D related
HLH	Hemophagocytoic lymphohistiocytosis

Abbreviation or Specialist Term	Explanation
HSCT	Hematopoietic stem cell transplantation
IAF	Informed assent form
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IFN	Interferon
IgG	Immunoglobulin G
[redacted]	
IL	Interleukin
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive response technology
IUD	Intrauterine device
IV	Intravenous (or intravenously)
IVIG	Intravenous immunoglobulins
kg	kilogram
LBL	Lymphoblastic lymphoma
LD	Lymphodepleting
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
LTLS	Laboratory tumor lysis syndrome
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mTPI-2	Modified toxicity probability interval
MRD	Minimal residual disease
MRI	Magnetic resonance imaging

Abbreviation or Specialist Term	Explanation
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
MTX	Methotrexate
MUGA	Multi-gated acquisition scan
MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NT	Neurotoxicity
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
[redacted]	
PCP	Pneumocystis pneumonia
PD	Progressive disease
PE	Pulmonary embolism
PedsQL	Pediatric quality of life
PK	Pharmacokinetic, pharmacokinetics
PMBCL	Primary mediastinal large B-cell lymphoma
PO	Per os, by mouth
[redacted]	
PQC	Product Quality Complaint
PR	Partial response
PRO	Patient reported outcome
ddPCR	Droplet digital polymerase chain reaction
RCL	Replication-competent lentivirus
RFS	Relapse-free survival
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
r/r	Relapsed/refractory
RSI	Reference Safety Information

Abbreviation or Specialist Term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
scFv	Single chain variable fragment
sCRS	Severe cytokine release syndrome
SCT	Stem cell transplantation
SEER	Surveillance, Epidemiology, and End Results
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
sNT	Severe neurotoxicity
SOP	Standard operating procedure
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SRC	Safety Review Committee
SSC	Scientific Steering Committee
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TKI	Tyrosine-kinase inhibitor
TLH	Trilineage hematopoiesis
TLS	Tumor lysis syndrome
TMG	Toxicity management guideline
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

APPENDIX B. RESPONSE CRITERIA FOR ALL

Response	Criteria
Complete response (CR)	No circulating blasts in the blood or bone marrow No extramedullary disease No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement Trilineage hematopoiesis (TLH) and < 5% Absolute neutrophil count (ANC) > 1000/µL Platelets > 100,000/µL No recurrence for 4 weeks
Complete response with incomplete blood count recovery (CRi)	Meets all criteria for CR except platelets ≤ 100,000/µL or ANC is ≤ 1000/µL
Refractory disease	Failure to achieve CR at the end of treatment
Progressive disease (PD)	Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
Relapsed disease[a]	Reappearance of blasts in the blood or bone marrow (> 5%) or > 1% with previous/supportive molecular findings or in any extramedullary site after a CR
MRD negative Complete Response (MRD-CR)	CR defined above with no MRD detected (< 0.01% by a validated assay)
MRD negative Complete Response with incomplete blood count recovery (MRD-CRi)	CRi defined above with no MRD detected (< 0.01% by a validated assay)

[a] MRD relapse is defined as an MRD detection by validated assay at a frequency of 1×10^{-4} or greater in BM cells following an initial MRD negative (less than 1×10^{-4}) CR/CRi.

Abbreviations: ANC = absolute neutrophil count; CNS = central nervous system; CR = complete response; CRi = complete response with incomplete blood count recovery; MRD = minimal residual disease; PD = progressive disease; TLH = trilineage hematopoiesis; µL = microliter.

Source: NCCN Response Criteria Guidelines for pediatric ALL (NCCN, 2019).

APPENDIX C. RESPONSE CRITERIA FOR NHL

Response	Criteria
Complete response (CR)	CT or MRI reveals no residual disease or new lesions Resected residual mass that is pathologically (morphologically) negative for disease BM and CSF morphologically free of disease
Partial response (PR)	50% decrease in SPD on CT or MRI No new lesions and/or PD Morphologic evidence of disease may be present in BM or CSF if present at diagnosis; however, there should be 50% reduction in percentage of lymphoma cells
Minor response (MR)	Decrease in SPD > 25% but < 50% on CT or MRI No new lesions and/or PD Morphologic evidence of disease may be present in BM or CSF if present at diagnosis; however, there should be 25% to 50% reduction in percentage of lymphoma cells
No response (NR)	For those who do not meet CR, PR, MR, or PD criteria
Progressive disease (PD)	For those with > 25% increase in SPD on CT or MRI, or Development of new morphologic evidence of disease in BM or CSF

Abbreviations: BM = bone marrow; CR = complete response; CSF = cerebrospinal spinal fluid; CT = computed tomography; MR = minor response; MRI = magnetic resonance imaging; NHL = non-Hodgkin lymphoma; NR = no response; PD = progressive disease; PR = partial response; SPD = sum of product of greatest perpendicular diameters

Source: International Pediatric NHL Response Criteria (2015) (Sandlund, 2015).

APPENDIX D. CLINICAL LABORATORY EVALUATIONS

Table 9: Clinical Laboratory Evaluations

Laboratory evaluations will be performed both centrally and locally according to Table 9. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs/SAEs or expected events. Clinical management of study subjects will be based on local assessments.

It is the responsibility of the Investigator to obtain and review laboratory results for subject safety and follow up with subjects in a timely manner.

Laboratory Panel	Analytes
Hematology	CBC with differential
Coagulation	PT, aPTT, INR, fibrinogen, and D-dimer
Chemistry	Glucose, BUN, creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), magnesium, phosphate, bicarbonate, LDH, uric acid, triglycerides
Immunoglobulins	IgG, IgM, IgA
Viral serology[b]	HIV Hepatitis B (HBsAb, HBsAg, and HBcAb), Hepatitis C (Hep C Ab)
Inflammatory markers	CRP, ferritin
HLA typing[a]	HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1
Donor chimerism[a]	% stem cell donor
Cerebrospinal fluid[a]	RBCs, WBCs with differential including leukemia/lymphoma cells (blasts),
Pregnancy[a]	ß-HCG (serum)

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; HBcAb = Hepatitis B core antibody HBsAb = Hepatitis B surface antibody; HBsAg = Hepatitis B surface antibody; HIV= Human Immunodeficiency Virus; HLA = Human leukocyte antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

[a] Local assessment only.

[b] For the assessment at the leukapheresis visit, refer to the [redacted] collection laboratory manual for further details on where sample is sent for analysis.

APPENDIX E. CAIRO-BISHOP DEFINITIONS OF TUMOR LYSIS SYNDROME

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Laboratory Parameter	Laboratory Result
Urate	≥ 476 μmol/L or 25% increase from baseline
Potassium	≥ 6.0 mmol/L or 25% increase from baseline
Phosphorous	≥ 2.1 mmol/L or 25% increase from baseline
Calcium	≤ 1.75 mmol/L or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of urate, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).

Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted)
2. Cardiac arrhythmia/sudden death[a]
3. Seizure[a]

Abbreviations: TLS = tumor lysis syndrome; ULN = upper limit of normal.
[a] Not directly attributable to a therapeutic agent.

Cairo-Bishop Grading System for TLS

Grade[b]	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 × ULN	None	None
1	+	1.5 × ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 × ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with activities of daily life (ADL)

Cairo-Bishop Grading System for TLS (Continued)

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
3	+	> 3.0 – 6.0 × ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 × ULN	Life-threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death[a]	Death[a]

Abbreviations: ADL = activities of daily living; LTLS = laboratory tumor lysis syndrome; TLS = tumor lysis syndrome; ULN = upper limit of normal.
[a] Probably or definitely attributable to clinical TLS.
[b] Clinical tumor lysis syndrome (CTLS) requires one or more clinical manifestations along with criteria for laboratory tumor lysis syndrome (LTLS). Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade.
Source: (Cairo, 2004).

APPENDIX F. MANAGEMENT GUIDELINES FOR CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES (PEDIATRICS VERSION 2.0)

MANAGEMENT OF TOXICITIES ASSOCIATED WITH JCAR017

Cytokine release syndrome (CRS) and neurologic toxicities (NT) are associated with CAR T cell therapies. Celgene has developed the toxicity management guidelines (TMG) for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs. These recommendations are based on the CRS revised grading system (Lee, 2014) and the Common Toxicity Criteria for Adverse Events (CTCAE) and need to be used for grading of CRS and NT to guide management in this trial.

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

1. CYTOKINE RELEASE SYNDROME

Administration of cellular products such as chimeric antigen receptor (CAR)-expressing T cells can be associated with cytokine-associated toxicity due to systemic production and release of various cytokines into the circulation. Cytokine-associated toxicity, also known as cytokine release syndrome (CRS), is a toxicity that occurs as a result of immune activation (Gardner, 2017; Lee, 2014).

1.1. Pathophysiology of Cytokine Release Syndrome

The hallmark of CRS is immune activation resulting in elevated inflammatory cytokines. Cytokine release syndrome clinically manifests when large numbers of lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. Cytokine release syndrome has classically been associated with therapeutic monoclonal antibody (mAb) infusions, most notably anti-CD3 (OKT3), anti-CD52 (alemtuzumab), anti-CD20 (rituximab), and the CD28 super-agonist, TGN1412. Cytokine release syndrome is also frequently observed following administration of bi-specific T cell engaging antibodies for leukemia, and adoptive cellular immunotherapies for cancer, most notably CAR T cells. Incidence, time to onset and severity of CRS due to CAR T cells is at least partially dependent on the infused cell dose and tumor burden/antigen density, presumably due to more rapid and higher levels of CAR T cell activation. Onset of CRS symptoms typically occurs days to occasionally weeks after the CAR T cell infusion, usually preceding maximal in vivo T cell expansion. Cytokine release syndrome is associated with elevated interferon gamma (IFN-γ), interleukin (IL)-6, and tumor necrosis alpha (TNFα) levels, and increases in IL-2, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-10, IL-8, IL-5, and fractalkine although the pattern of elevated cytokines varies among subjects (Davila, 2014; Hay, 2017). Interleukin 6 has been identified as a central mediator of toxicity in CRS. Interleukin 6 is a pleiotropic cytokine with anti-inflammatory and proinflammatory properties. High levels of IL-6, present in the context of CRS, likely initiates a proinflammatory IL-6-mediated signaling cascade.

1.2. Clinical Presentation of Cytokine Release Syndrome

Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (Lee, 2014), and management can be complicated by concurrent conditions. In non-Hodgkin lymphoma (NHL) subjects treated with JCAR017, CRS usually occurs within two weeks after infusion (Abramson, 2017).

- Fever, especially high fever (≥ 38.5°C or ≥ 101.3°F), is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms, and appropriate cultures must be obtained, and empiric antibiotic therapy initiated per institution standard of care.
- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurologic toxicity has been observed concurrently with CRS; refer to Section 3 below.

- With other CAR T cell products, CRS has been reported in a few cases to be associated with findings of macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), and the physiology of the syndromes may overlap.

1.3. Clinical Management of Cytokine Release Syndrome

Across various CAR T cell products, early manifestations of CRS can predict more severe toxicity for both CRS and neurotoxicity (NT).

Subjects with B-cell acute lymphoblastic leukemia (B-ALL) and high burden of disease are at high risk of developing CRS (Frey, 2017). Subjects with NHL who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters [SPD] or high serum lactate dehydrogenase [LDH; ≥ 500 U/L prior to the start of lymphodepletion] also have a higher risk for developing CRS and/or neurotoxicity (Siddiqi, 2017).

High baseline levels of other commonly measured inflammatory markers, such as ferritin and C-reactive protein (CRP), were also associated with CRS.

It should be noted that, although useful for identifying subjects at higher risk for developing CRS, CRP, ferritin, and serum cytokine levels should not be used for CRS clinical management/treatment decisions in the absence of other clinical signs and symptoms of CRS; for example, a subject with an elevated CRP but no concomitant symptoms may not require intervention (Park, 2017). Thus, close observation of these subjects is strongly recommended.

A modification of the Common Toxicity Criteria for Adverse Events (CTCAE) CRS grading scale has been established to better reflect CAR T cell-associated CRS, as detailed in Table 10 (Lee, 2014).

Table 10: Grading Criteria for Cytokine Release Syndrome

	Symptoms/Signs	Cytokine Release Syndrome (CRS) Grade 1 (mild)	CRS Grade 2 (moderate)	CRS Grade 3 (severe)	CRS Grade 4 (life-threatening)
			CRS grade is defined by the most severe symptom (excluding fever)		
Vital Signs	Temperature ≥ 38.5°C/101.3°F	Yes	Any	Any	Any
	Systolic blood pressure (SBP) ≤ 90 mm Hg	N/A	Responds to intravenous (IV) fluids or single low-dose vasopressor	Needs high-dose[a] or multiple vasopressors	Life-threatening
	Need for oxygen to reach oxygen saturation (SaO_2) > 90%	N/A	Fraction of inspired oxygen (FiO_2) < 40%	FiO_2 ≥ 40%	Needs ventilator support
Organ Toxicity		N/A	Grade 2	Grade 3 or transaminitis Grade 4	Grade 4 (excluding transaminitis)

[a] Definition of high-dose vasopressors in Table 11 .

Table 11: High-Dose Vasopressors (all doses required for ≥ 3 hours)

Vasopressor	Dose
Norepinephrine monotherapy	≥ 0.2 µg/kg/min up to 50 kg, then flat 10 µg/min for > 50 kg
Dopamine monotherapy	≥ 10 µg/kg/min up to 50 kg, then flat 500 µg/min for > 50 kg
Phenylephrine monotherapy	4 µg/kg/min up to 50 kg, then flat 200 µg/min for > 50 kg
Epinephrine monotherapy	≥ 0.1 µg/kg/min up to 50 kg, then flat 5 µg/min for > 50 kg
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 0.1 µg/kg/min[a]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 µg/min[a]

[a] VASST Trial Vasopressor Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10]

Note: Pediatric weight adjustments should be taken into consideration
Adapted from (Lee, 2014).

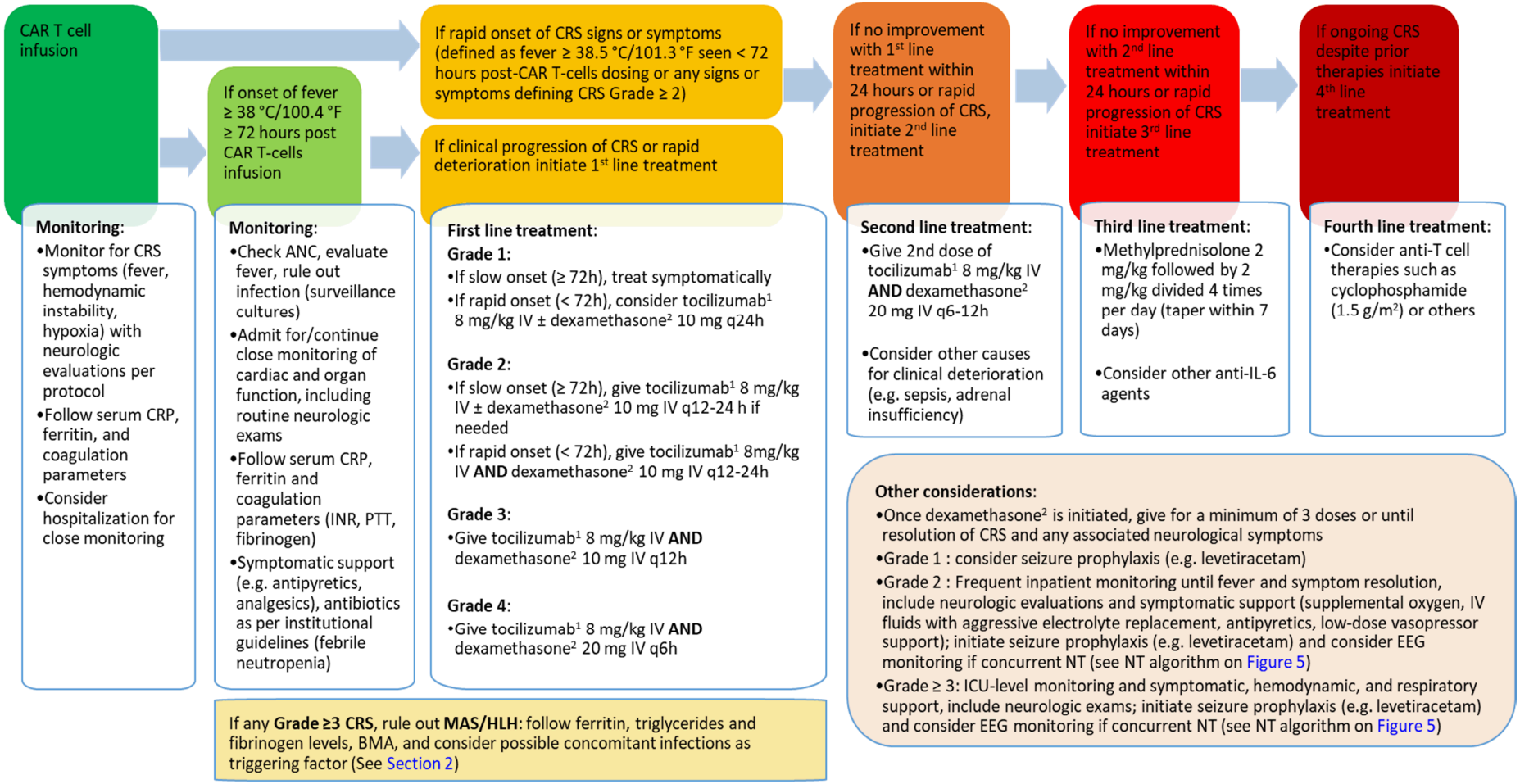
Detailed CRS management guidelines are shown in Figure 4. Treatment should be individualized for each subject's clinical needs (note: For pediatric subjects, please refer to the package insert for the appropriate pediatric dosing for treatments outlined in Figure 4). This guidance emphasizes the importance of early intervention for Grade 2 CRS, or in the setting of a rapid onset or rapid progression of CRS symptoms, to prevent the development of severe (Grade 3 or greater) CRS and NT.

In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe CRS. Please refer to the currently approved Actemra® prescribing information (US) or RoActemra® Summary of Product Characteristics (EU). Actemra® has been approved by the Food and Drug Administration (FDA) for the treatment of CAR T cell-induced severe or life-threatening CRS in adults and pediatric subjects 2 years of age and older. RoActemra® has been approved by the European Medicines Agency (EMA) for the treatment of CAR T cell-induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older. The preferred dose to intervene in adult subjects with CRS is 8 mg/kg (maximum 800 mg) IV. In pediatric subjects above 2 years of age, the recommended dose is 8 mg/kg in subjects weighing greater than or equal to 30 kg, or 12 mg/kg in subjects weighing less than 30 kg. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, additional doses of tocilizumab may be administered (Please see Figure 4, Actemra® prescribing information [US] and RoActemra® Summary of Product Characteristics [EU]).

Other anti-IL-6 agents, if available in the country, should be considered in the event of severe CRS not responding to tocilizumab and corticosteroids. Dosing of any other anti-IL-6 agent should be per prescribing information.

In the most unresponsive severe cases additional treatments with T cell depleting therapies such as cyclophosphamide should be considered (Brudno, 2016).

Figure 4: JCAR017 Cytokine Release Syndrome Treatment Algorithm



Abbreviations: ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CRP = C-reactive protein; CRS = cytokine release syndrome; EEG = electroencephalogram; ICU = intensive care unit; IL-6 = interleukin 6; INR = international normalized ratio; IV = intravenous; NT = neurotoxicity; PTT = partial thromboplastin time; q = every; MAS/HLH = macrophage activation syndrome/Hemophagocytic Lympho-histiocytosis.

NOTE

1. Tocilizumab dose should be adjusted to 12 mg/kg in subjects weighing < 30 kg.
2. In pediatric subjects, the recommended dexamethasone dosing is as follows: **10 mg adult equivalent for pediatrics: 0.2 mg/kg** up to 50 kg, then flat 10 mg thereafter; **20 mg adult equivalent for pediatrics: 0.4 mg/kg** up to 50 kg, then flat 20 mg thereafter.

2. MACROPHAGE ACTIVATION SYNDROME (MAS)/HEMOPHAGOCYTIC LYMPHO-HISTIOCYTOSIS (HLH)

Macrophage Activation Syndrome (MAS) or Hemophagocytic Lympho-histiocytosis (HLH) is a rare, potentially fatal immune-mediated disease, caused by impaired natural killer and cytotoxic T-cell function. This syndrome has a wide range of causes, symptoms, and outcomes, but all lead to a hyperinflammatory response (with some characteristics that overlap with Cytokine Release Syndrome, CRS) and organ damage (Ramos-Casals, 2014). Cases of HLH have been described in patients treated with CAR T therapies.

2.1. Pathophysiology of HLH/MAS

MAS/HLH is divided into primary (genetic) and secondary (reactive) forms. Secondary MAS/HLH is subclassified as viral, autoimmune, or tumor related. MAS/HLH has both infectious and non-infectious triggers (Ramos-Casals, 2014). Viral infection is the most frequent trigger, either due to primary infection or after reactivation in immunosuppressed patients. Bacterial and fungal infections can also trigger MAS/HLH. Macrophage Activation Like Syndrome (MALS) is a distinct entity that leads to early death in septic patients and must be carefully ruled out in patients who are prone to develop severe infections, including patients following CAR T cell therapy (Karakike, 2019). Patients with cancer, mainly those with hematological malignancies, and in particular lymphoma, have a higher risk of developing MAS/HLH.

A defect in granule-mediated cytotoxicity is the underlying common mechanism in both primary and secondary forms of MAS/HLH (Ramos-Casals, 2014; Crayne, 2019). Enhanced antigen presentation and repeated interferon γ-dependent stimulation of Toll-like receptors are postulated as causal mechanisms of the uncontrolled activation of antigen-presenting cells and T cells (Behrens, 2011). This activation produces an overshooting of inflammatory response caused by hypersecretion of proinflammatory cytokines such as interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), interleukin 1, interleukin 4, interleukin 6, interleukin 8, interleukin 10 and interleukin 18. This so-called cytokine storm contributes to tissue damage and progressive systemic organ failure (Crayne, 2019).

2.2. Clinical Presentation and Diagnosis of HLH/MAS

The presentation of secondary MAS/HLH is heterogeneous and characterized by a panoply of clinical signs and symptoms. The clinical syndrome can be acute or subacute with non-specific symptoms appearing over days to week(s) (Ramos-Casals, 2014). The cardinal features are continuous high fever (≥ 38.5 °C) and enlarged lymphohematopoietic organs (spleen/hepatomegaly, occasionally accompanied by adenopathy). Pulmonary involvement is frequent (42%), symptoms may include cough, dyspnea, and respiratory failure. Neurologic presentation (25%) are heterogeneous and may include coma, seizures, meningitis and encephalomyelitis. Twenty-five percent of patients also have non-specific cutaneous involvement, including erythematous rashes, edema, petechiae, and/or purpura. Gastrointestinal symptoms (18%) include diarrhea, nausea, vomiting and/or abdominal pain.

Laboratory markers associated with MAS/HLH are as follows:

- Thrombocytopenia and anemia are identified in almost 80% of adult cases, and leukopenia in 69%. Most of the cases are grade 3 or 4 according to CTCAE v4.03.
- Hyperferritinaemia is a key diagnostic test: 90% of adult patients with MAS/HLH have increased concentrations, and 25% may reach very high levels ≥ 22,000 ng/mL.
- Almost 60% of patients have coagulation disorders related to liver dysfunction. Hypofibrinogenemia and raised D-dimer levels are reported in 50% of cases.
- Hypertriglyceridemia is identified in 69% of adults with HLH and has been associated with lipoprotein lipase inhibition caused by excess TNF-α.
- Nearly 80% of patients have abnormalities in liver function (increased alkaline phosphatase and transaminase levels in 71% and 57%, respectively). Increased serum lactate dehydrogenase concentrations are reported in 78% of patients.

Detection of any ongoing infection acting as a trigger for MAS/HLH is critical. Standard tests should be used to screen for infections caused by the most common viruses such as herpes, CMV and EBV. Other infectious agents (eg, mycobacteria, parasites, and fungi, particularly Candida and Mucor) should be ruled out according to specific clinical or epidemiological features (Ramos-Casals, 2014; Lehmberg, 2015).

The abnormal immunological response caused by MAS/HLH can be measured either serologically or through functional cellular assays. High serum concentrations of soluble CD25 (interleukin 2 receptor α) occur in 79% of cases of HLH. Low or absent NK cell cytotoxicity is a criterion for diagnosis of MAS/HLH. NK cell function can be assessed with a variety of methods (chromium 51 assays, CD107a externalization), though these techniques have not been standardized yet (Ramos-Casals, 2014; Lehmberg, 2015).

Bone marrow is the preferred anatomical site for investigation of suspected MAS/HLH, with bone marrow aspirates (BMA) in 84% of adult cases showing evidence of hemophagocytosis. Hemophagocytosis can also occur in the reticuloendothelial organs (lymph nodes, spleen, and liver). BMA can be negative at the initial stage of HLH and should be repeated during the clinical course if there is a high suspicion of HLH.

The diagnosis of MAS/HLH (according to HLH-2004 consensus criteria, further revised in 2014 for HLH associated with malignancies) (Lehmberg, 2015) can be established if one of either of the criteria below is fulfilled:

(1) A molecular diagnosis consistent with HLH

(2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below):

- High persistent fever (≥38.5 °C)
- Splenomegaly
- Cytopenias (affecting 2 of 3 lineages in the peripheral blood): Hemoglobin < 90 g/L, platelets < 100 x 10^9/L, neutrophils < 1.0 x 10^9/L
- Triglycerides ≥ 3.0 mmol/L (ie, 265 mg/dL) or fibrinogen ≤ 1.5 g/L
- Hemophagocytosis in bone marrow, spleen and/or lymph nodes

- Low or absent NK-cell activity (according to local laboratory reference)
- Ferritin ≥ 500 ng/mL
- Soluble CD25 (ie, soluble IL-2 receptor) ≥ 2,400 U/mL

2.3. Clinical Management of HLH/MAS

Effective treatment of HLH requires multiple simultaneous approaches (Ramos-Casals, 2014; Lehmberg, 2015).

1. Supportive care is essential because of frequent life-threatening severe manifestations at presentation.
2. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation. Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis and treatment must be initiated.
3. Suppression of the inflammatory response and cell proliferation by immunosuppressive and cytotoxic drugs, respectively, is necessary. First line treatment includes IL-6-blockade with tocilizumab. Glucocorticoids are also indicated for the initial treatment of MAS/HLH, irrespective of the cause (CRS grade 4 algorithm should be followed). IL-1 blockade with anakinra is suggested as second line treatment or in case of rapidly progressing clinical course. Siltuximab might be considered as well as second line therapy. The use of cyclosporin, cyclophosphamide, etoposide and/or intrathecal methotrexate is not generally indicated in patients who develop MAS/HLH after CAR T therapy, but may have to be employed in refractory cases, when prolonged high-dose steroid treatment combined with cytokine blockers have previously failed. Newer emerging treatments might also be considered (although their value has not yet clearly been demonstrated), including lenzilumab (anti-GMCSF antibody) (Sterner, 2019) and emapalumab (anti-IFNγ antibody), the latter having been recently approved by FDA for the treatment of adult and pediatric patients with primary HLH with refractory, recurrent or progressive disease or intolerance to conventional HLH therapy (Benedetti, 2019). Platelet transfusions, fresh frozen plasma and/or activated factor VIII might be needed for patients with life-threatening acute bleeding. Growth factors such as granulocyte colony stimulating factor might be used for severe neutropenia.

3. NEUROLOGIC TOXICITIES

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

3.1. Pathophysiology of Neurologic Toxicities

The pathogenesis of neurotoxicity is poorly defined. Analysis of a subset of subjects treated with JCAR017 (study 017001 - TRANSCEND NHL001) with NHL who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters or high serum LDH [≥ 500 U/L] prior to the start of lymphodepletion) also have a higher risk for developing neurotoxicity (Siddiqi, 2017). In addition, severe neurotoxicity has also been reported in subjects with B-ALL and higher disease burden at the time of CD19 directed CAR T cell infusion (Gust, 2017; Park, 2017).

Recent experimental models point to an important role of IL-1 in the initiation of inflammatory changes that lead to neurotoxicity (Norelli, 2018; Giavridis, 2018). Peak levels of IL-6, IFN-γ, ferritin, and CRP are significantly higher in subjects who develop any grade or Grade 3 or higher neurotoxicity (Heipel, 2017; Turtle, 2016a). Protein levels in the cerebrospinal fluid (CSF) are usually elevated in patients with neurotoxicity, compared with baseline measurements, suggesting disruption of the blood-brain barrier. Other organ dysfunction (hepatic and renal), as well as hypoxemia, and infection, might also contribute to the encephalopathy (Neelapu, 2018). In another study, it has been reported that evidence for cytokine-mediated endothelial activation causes coagulopathy, capillary leak, and blood-brain barrier disruption allowing transit of high concentrations of systemic cytokines into the CSF (Gust, 2017).

3.2. Clinical Management of Neurologic Toxicities

The optimal management of CAR T cell-induced neurotoxicity is unknown at this time. These management guidelines represent the current state of knowledge and additional information will be provided to Investigators as it becomes available. Medical Monitor should be contacted immediately as soon as neurological symptoms occur. Management should follow the guidelines provided below and may include additional measures as per institutional or standard clinical practice, and as determined by the Investigator or treating physician and/or consulting neurologist. A thorough neurologic evaluation should be pursued and additional evaluations, including electroencephalogram (EEG), magnetic resonance imaging (MRI) or computer tomography (CT) scan of the brain and diagnostic lumbar puncture and frequent monitoring of cognitive function (eg, mini mental status exams or handwriting tests) should be considered.

Treatable causes of neurologic dysfunction, such as infection or hemorrhage should be ruled out. Common manifestations of neurotoxicity (eg, confusion, seizure, aphasia), can also be seen with infection, electrolyte imbalances, metabolic acidosis, uremia, concomitant medication use (eg, narcotics), and other medical conditions. Other causes for such symptoms should be considered.

Not all symptoms may be due to CAR T-induced neurotoxicity. For example, headaches are common in this population. Headaches alone might suggest the need for imaging but may not need to trigger escalating therapy unless there are other findings suggestive of neurotoxicity.

Magnetic resonance imaging and CT scans of the brain are usually negative for any anatomical pathology that would account for the neurotoxicity symptoms observed in subjects treated with CAR T cell therapy, although rare cases of reversible T2/fluid attenuated inversion recovery (FLAIR) MRI hyperintensity involving the thalami, dorsal pons, and medulla, and cerebral edema have been reported (Neelapu, 2018).

For subjects who have neurologic toxicity in the presence of CRS, the CRS should be managed following the guidelines provided in Figure 4.

Neurotoxicity should be graded per CTCAE v4.03 and managed following the guidelines provided in Figure 5. For concurrent CRS and neurotoxicity, the most aggressive intervention recommended by either guideline should be employed (if the recommendations for steroid doses differ, use the highest dose and/or frequency). For subjects with Grade 4 neurotoxicity with cerebral edema, high-dose corticosteroids, hyperventilation and hyperosmolar therapy have been recommended (Neelapu, 2018).

Note: Tocilizumab is not recommended for the treatment of neurotoxicity related to CAR T cell therapy, unless CRS or MAS/HLH is also present. Results from 2 studies, one of preemptive use of tocilizumab shortly after anti-CD19 CAR T cell therapy in relapsed/refractory NHL subjects (Locke, 2017), and the other mandatory use of tocilizumab at first fever [> 38.5°C] in pediatric ALL patients treated with anti-CD19 CAR T cells (Gardner, 2016), demonstrated that early tocilizumab use either increased overall neurotoxicity and Grade ≥ 3 neurotoxicity rates (85% versus 62% overall; 35% versus 26% Grade ≥ 3) or provided no improvement in neurotoxicity rates, respectively. These findings support the hypothesis that tocilizumab does not improve and may worsen isolated neurotoxicity (Locke, 2017).

Neurotoxicity management guidelines are provided in Figure 5. For pediatric studies, please refer to the package insert for the appropriate pediatric dosing for treatments outlined in Figure 5.

If neurotoxicity occurs, anti-seizure prophylaxis should be initiated, and dexamethasone should be used as per the NT algorithm in Figure 5. Interventions are guided by timing of preceding fever, if any. Early onset of fever within 3 days, particularly if high (≥ 39°C) (Gust, 2017), will trigger shorter intervals between dexamethasone administrations. If no improvement to the highest dose of dexamethasone 0.4 mg/kg q6, consider the use of methylprednisolone 2 mg/kg loading dose followed by 1 mg/kg q6 per day.

Closely monitor for rapid neurological deterioration, especially if neurotoxicity of Grade 0 or Grade 1 is shifting to obtundation within a few hours. In such a situation, high clinical suspicion of cerebral edema (CE) is warranted independently of a CT/MRI confirmed diagnosis. The subject should immediately be transferred to the ICU and the below recommended measures should be instituted (see also Figure 6), after consulting with the Celgene Medical Monitor as soon as possible:

4. Maximal medical support should be given, such as anti-seizure medications, mannitol/hypertonic fluids and sedation.

5. Appropriate diagnostic measures should be performed as quickly as possible, including intracranial pressure (ICP) measurement (neurosurgical consult), lumbar puncture if feasible and safe (for cytology, culture, pharmacokinetics [PK] and cytokines), serum PK and cytokines, MRI and EEG.
6. Give methylprednisolone IV 20 mg/kg x 1
7. If CRS/MAS present: give anti-cytokine therapy*

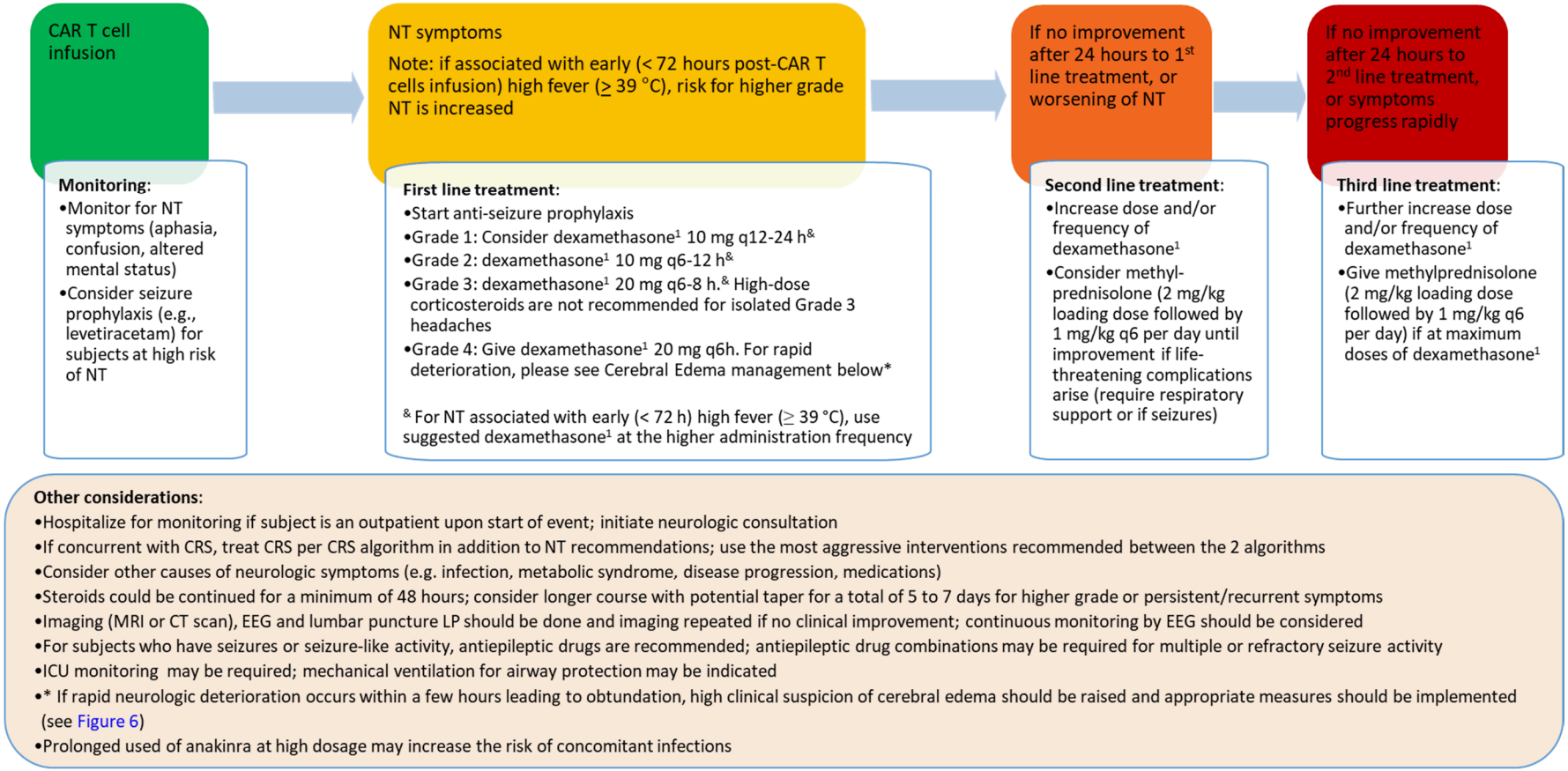
If after 24 hours there is continued clinical suspicion of CE or once CE is documented:

1. Maximal medical support should be continued, including intubation plus hyperventilation.
2. Continue methylprednisolone 20-30 mg/kg IV qd and anti-cytokine therapy** until improvement, then taper methylprednisolone slowly over 1 week to avoid rebound neurotoxicity.
3. Consider cyclophosphamide 1.5 g/m^2 IV as single administration.

*Anakinra 2 mg/kg SQ q8. Also, consider IL-6 blockade with siltuximab 11 mg/kg IV qd. Tocilizumab should NOT be used.

**Anakinra higher dosing may be necessary if no response and according to evolution and severity of the clinical picture: upon discussion with the Medical Monitor anakinra can be increased up to 10 mg/kg IV or SQ q6. Anakinra should be maintained until clear improvement, and, after initiating tapering methylprednisolone, should be administered at a standard dose of 2 mg/kg/day SQ and stopped after discontinuation of methylprednisolone. Please consider that prolonged use of anakinra at high dosage may increase the risk of concomitant infections.

Figure 5: Neurotoxicity Treatment Algorithm



Abbreviations: CAR = chimeric antigen receptor; CE= cerebral edema; CRS = cytokine release syndrome; CT = computed tomography; EEG = electroencephalogram; ICP = intracranial pressure; ICU = intensive care unit; IV = intravenous; LP = lumbar puncture; MRI = magnetic resonance imaging; NT = neurotoxicity; PK = pharmacokinetics; q = every.

NOTE:

1. In pediatric subjects, the recommended dexamethasone dosing is as follows: **10 mg adult equivalent for pediatrics: 0.2 mg/kg** up to 50 kg, then flat 10 mg thereafter; **20 mg adult equivalent for pediatrics: 0.4 mg/kg** up to 50 kg, then flat 20 mg thereafter.

Figure 6: Cerebral Edema Management Guidelines

Cerebral Edema (CE): If suspected, the subject should immediately be transferred to the ICU and the below recommended measures should be instituted (see **Section 2.2** for details):

1. Maximal medical support, such as anti-seizure medications, mannitol/hypertonic fluids, intubation plus hyperventilation and sedation
2. Diagnostic measures should be performed (LP, serum PK/cytokines, ICP measurement, MRI/EEG).
3. Methylprednisolone 20 mg/kg qd until improvement, taper slowly over 1 week
4. Anti-cytokine therapy (anakinra, siltuximab) until improvement, stop only after tapering methylprednisolone
5. Cyclophosphamide 1.5 g/m^2 IV as single administration, once CE is confirmed/documented, if no improvement

Abbreviations: CE = cerebral edema; EEG = electroencephalogram; ICP = intracranial pressure; ICU = intensive care unit; IV = intravenous; LP = lumbar puncture; MRI = magnetic resonance imaging; PK = pharmacokinetics; qd = every day.

4. REFERENCES

Abramson JS, Palomba ML, Gordon LI, Lunning MA, Arnason JE, Wang M, et al. High durable CR rates in relapsed/refractory (r/r) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort. Blood. 2017 Dec 7;130(1): Abstract No. 581.

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

Behrens EM, Canna SW, Slade K, et al. Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. J Clin Invest 2011; 121: 2264–77.

Benedetti FD, Brogan P, Grom A, et al. OP0204 Emapalumab, an intrerferon gamma (IFN-Y)-blocking monoclonal antibody, in patients with macrophage activation syndrome (MAS) complicatin systemic juvenile idiopathic arthritis (SJIA). Annals of the Rheumatic Diseases 2019;78:178.

Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321-30.

Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. Front Immunol. 2019 Feb 1;10:119.

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

Frey N. Cytokine release syndrome: Who is at risk and how to treat. Best Pract Res Clin Haematol. 2017 Dec;30(4):336-40.

Gardner R, Leger K, Annesley C, Summers C, Rivers, J., Gust J, et al. Decreased Rates of Severe CRS seen with early intervention strategies for CD19 CAR-T cell toxicity management. Blood. 2016; 128(22): 586.

Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129(25):3322-31.

Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Piersigilli A, Sadelain M. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med. 2018 Jun;24(6):731-738.

Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov. 2017 Dec; 7(12):1404-19.

Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood. 2017 Nov 23;130(21):2295-306.

Heipel M, Smith J, Brown W, Karimi M, Xie B, Li D, et al. Pharmacokinetic, pharmacodynamic and blood analytes associated with clinical response and safety in relapsed/refractory aggressive B-NHL patients treated with JCAR017. Blood. 2017 Dec 7;130(1): 2835.

Karakike E and Giamarellos-Bourboulis EJ. Macrophage Activation-Like Syndrome: A Distinct Entity Leading to Early Death in Sepsis. Front Immunol. 2019 Jan 31;10:55.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-195. Erratum in: Blood. 2015;126(8):1048.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019, Apr;25(4):625-38.

Lehmberg K, Nichols KE, Henter JI, et al. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica. 2015 Aug;100(8):997-1004.

Locke FL, Neelapu SS, Bartlett NL, Lekakis LJ, Jabobson CA, Braunschweig I, et al. Preliminary results of prophylactic tocilizumab after axicabtagene ciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-Hodgkin lymphoma (NHL). Blood. 2017 Dec 7;130(1): Abstract 1547.

Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.

Norelli M, Camisa B, Barbiera G, Falcone L, Purevdorj A, Genua M, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med. 2018 Jun;24(6):739-748.

Park JH. Managing Cytokine Release Syndrome. Clinical Care Options Oncology [Internet]. 2017; https://www.clinicaloptions.com/Oncology/Treatment Updates/Managing AEs/Modules/Managing_CRS.aspx.

Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Lancet. Adult haemophagocytic syndrome. 2014 Apr 26;383(9927):1503-1516. Erratum in: Lancet. 2014 Apr 26;383(9927):1464.

Rosalie M. Sterner, Reona Sakemura, et al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. Blood. 2019 Feb 14;133(7):697-709.

RoActemra® [Summary of Product Characteristics]. Welwyn Garden City, United Kingdom: Roche Products Limited. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf.

Siddiqi T, Abramson JS, Li D, Brown W, Devries T, Dave K, et al. Patient characteristics and pre-infusion biomarkers of inflammation correlate with clinical outcomes after treatment with the defined composition, CD19-targeted CAR T cell product, JCAR017. Blood. 2017; 130(1): Abstract 193.

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

APPENDIX G. MODIFIED TOXICITY PROBABILITY INTERVAL DECISION TABLE

Number of Patients

Number of Patients with DLTs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		D	D	D	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	D	D	D	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	D	D	D	S	S	S	S	S	E	E	E	E	E	E	E	E
5					DU	DU	DU	DU	DU	D	D	D	D	D	S	S	S	S	S	S	E	E	E	E
6						DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
14														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
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Sample size = **24** , Target toxicity probability = **30%** , epsilon 1 = **0.05** , epsilon 2 = **0.05**

E: Escalate to the next higher dose; **S**: Stay at the same dose; **D**: De-escalate to the previous lower dose; **DU**: De-escalate to the previous lower dose and the current dose will never be used again in the trial;

Celgene Signing Page

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

UserName: [redacted]
Title: [redacted]
Date: Monday, 16 September 2019, 01:23 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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SUMMARY OF CHANGES

AMENDMENT NO. 2.0

A PHASE 1/2, OPEN-LABEL, SINGLE ARM, MULTICOHORT, MULTICENTER TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF JCAR017 IN PEDIATRIC SUBJECTS WITH RELAPSED/REFRACTORY B-ALL AND B-NHL (TRANSCEND PEDALL)

INVESTIGATIONAL PRODUCT (IP):	**JCAR017**
PROTOCOL NUMBER:	**JCAR017-BCM-004**
ORIGINAL DATE:	**29 March 2018**
AMENDMENT No. 1.0 DATE:	**07 January 2019**
AMENDMENT No. 2.0 DATE:	**10 September 2019**
EudraCT NUMBER:	**2018-001246-34**
IND NUMBER	**016506**

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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

1. JUSTIFICATION FOR AMENDMENT

A global protocol Amendment of JCAR017-BCM-004 was prepared primarily to address:

- Commitments made following the initial clinical trial authorization (CTA) review by national competent authorities in Europe.
- Revisions made to the Phase 1 study design
- Additional details and updates regarding objectives, endpoints, study populations, sample size justification and statistical analyses

Significant changes included in this amendment are summarized below:

- **Revised Phase 1b trial design to Phase 1 dose finding with new starting dose**

  SCRI-CAR19v1, a chimeric antigen receptor (CAR) T cell product that is similar to JCAR017, has been well tolerated at doses from 0.5 x 10^6 to 1 x 10^6 CAR+ T cells/kg in pediatric subjects with B-cell acute lymphoblastic leukemia (B-ALL) (PLAT-02). While the PLAT-02 trial demonstrated encouraging clinical activity with an overall manageable toxicity profile in pediatric B-ALL, it should be noted that manufacturing process changes were needed to standardize JCAR017 product consistency and process robustness are necessary to support the conduct of the trial at multiple clinical sites with a global manufacturing process.

  An adverse event (Grade 4 neurotoxicity) observed in the first pediatric subject with B-ALL dosed in JCAR017-BCM-004 prompted Celgene to re-evaluate the dosing strategy. Analysis of the JCAR017 manufactured product characteristics showed very active CAR T+ cells as a result of the necessary process manufacturing modifications, suggesting that a lower safe starting dose should be identified. Trials using a defined composition product autologous CD8+CAR+ and CD4+CAR+ T cells that express a CD19-specific CAR such as JCAR014 (Turtle, 2016) and SCRI-CAR19v1 (Gardner, 2017) suggests that a 10-fold dose reduction significantly reduced toxicity while preserving efficacy and maintaining a positive risk/benefit.

  Based on these considerations, an initial Phase 1 dose finding/escalation with a 10-fold dose reduction to starting dose of 0.05×10^6 CAR T cells/kg will be pursued. If this dose is confirmed to be safe and tolerable, additional subjects will be enrolled at higher dose(s) up to 0.75 x10^6 CAR+ T cells/kg utilizing an mTPI-2 algorithm with the aim to identify the Recommend Phase 2 Dose (RP2D). Additional changes that are designed to assure safe administration of JCAR017 in the pediatric B-ALL setting are increased frequency of cytokine and PK determinations (to allow comprehensive subject data assessment during dose escalation) and modification of the toxicity management algorithm incorporating the learnings from diagnosis and management of the first subject dosed in the study.

  Revised Sections: Title Page; Protocol Summary; Section 1.3.2.1, Phase 1; Section 1.3.3.1 Rational for JCAR017 Dose; Section 3.1.1, Study Design (Phase 1); Figure 1, Overall Study Design; Section 4.1, Number of Subjects; Section 7.2.4, JCAR017 Administration; Section 7.2.5.1, JCAR017 Dose Levels and Schedule (Phase 1); Section 7.2.5.1.1, mTPI-2 Dose Escalation Decision Pathway (Dose Level 1); Section 7.2.5.1.2, Intra-Patient Dose Escalation; Section 9.1.1, Statistical Considerations Overview (Phase 1); Section 9.2.3, Dose-

limiting Toxicity Analysis Population; Section 9.3.1, Sample Size and Power Considerations (Phase 1); Section 9.7.1.1, Recommended Phase 2 Dose; Appendix G, Modified Toxicity Probability Interval Decision Table.

- **Best overall response (BOR) was added as a secondary endpoint for B-cell non-Hodgkin lymphoma (B-NHL) subjects**

  To further support the secondary objective to evaluate the efficacy of JCAR017 in B-NHL subjects, response assessments were added at Months 3, 6, 9 and as clinically indicated until End of Study (EOS).

  Revised Sections: Protocol Summary; Section 2, Table 1 (Study Objectives); Section 2, Table 2 (Study Endpoints); Section 5, Table 3; Section 6.10.2, Non-Hodgkin Lymphoma (B-NHL); Section 9.6.2.8, Best Overall Response Rate.

- **Eligibility Criteria**

  - **Updated lower weight limit to 6 kg for all JCAR017 dose levels**

    Revised Sections: Section 4.2, Inclusion Criteria #1

  - **Clarification of the therapeutic setting of minimal residual disease (MRD+) B-ALL, defined as:**

    - *"< 5% lymphoblasts by morphology with*
    - *MRD detected by a validated assay at a frequency of 1 x10^{-4} or greater in BM cells. Subjects eligible for enrollment in Cohort 2 are those with MRD positive morphologic CR2 after re-induction when these subjects had previously experienced an early relapse (< 36 months) after first-line chemotherapy. Subjects who are in MRD+ morphologic CR3 and later, regardless of time to relapse in earlier lines, are also eligible."*

    Revised Sections: Section 4.2, Inclusion Criteria #7

  - **A note was added for selection of subjects in Cohort 3 (pediatric relapsed/refractory [r/r] B-NHL) with secondary central nervous system (CNS) involvement**

    "Note: B-NHL subjects with secondary CNS lymphoma involvement are eligible however subject selection must consider clinical risk factors for severe neurological AEs and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject."

    Revised Sections: Section 3.1.2, Study Design (Phase 2); Section 4.2, Inclusion Criteria #7

  - **Updated Inclusion Criteria #11, #12 and #13 to align with the summary of product characteristics (SMPC) and US package insert (USPI) pregnancy guidance for cyclophosphamide. In addition, eliminated the exemption from using contraception, and abstaining from breastfeeding, based on testing for absence of residual JCAR017 CAR T cell persistence.**

    There is no exposure data to provide a recommendation concerning duration of contraception following treatment with JCAR017. The JCAR017 program is excluding pregnant subjects from participation and is mandating highly effective contraception to be used. So far, no

pregnancy occurred in the JCAR017 clinical development program. No animal studies have been conducted with JCAR017 to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether JCAR017 has the potential to be transferred to the fetus via the placenta and could cause fetal toxicity, including B-cell lymphocytopenia. As the risk for the becoming mother and the fetus/newborn is unknown at this time, and a negative qPCR test does not reliably predict complete disappearance of CAR T cells in the body, it cannot be used to guide duration of contraception. Therefore, the requirement for two subsequent negative qPCR test was removed.

Revised Sections: Section 4.2, Inclusion Criteria #11, #12 and #13; Section 6.1.4, Pre-Treatment Evaluation; Section 6.2.2, Post-Treatment Period; Section 10.4, Pregnancy

- **Subjects must be clinically stable prior to receiving lymphodepleting (LD) chemotherapy and JCAR017 infusion**

  To improve subject safety based on observations in other JCAR017 studies, treating physicians must evaluate a subject's medical condition to assess recovery from prior toxicities and exclude significant worsening in clinical status when compared to initial eligibility criteria at time of LD chemotherapy and of JCAR017 infusion.

  In addition, clarified that in the absence of infection, isolated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) elevation that can be linked temporally to administration of medication (eg, fungal prophylaxis or bridging chemotherapy) may not preclude treatment of subjects (LD chemotherapy and infusion of JCAR017) after discussion with Celgene's Medical Monitor.

  Revised Sections: Section 6.2.1.1, Criteria for Treatment

- **Added history or presence of cerebral edema to the list of exclusionary CNS pathologies**

  Revised Sections: Section 4.3, Exclusion Criteria #14.

- **Added existence of CD19 negative clone as an exclusionary criterion**

  Revised Sections: Section 4.3, Exclusion Criteria #19

- **Added safety monitoring boundaries**

  Safety monitoring boundaries that will be used to establish a Bayesian framework (ie, Thall and Simon stopping boundaries) have been added to help detect safety signals that may occur in the study.

  Revised Sections: Protocol Summary; Section 3.3, Safety Monitoring Boundaries

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

- Revised protocol throughout to align with Celgene protocol template
- Revised protocol summary to align with protocol title page
- "CD4+" and "CD8+" were replaced with "CD4+CAR+" and "CD8+CAR+", respectively
- Clarified throughout protocol that subjects will be followed "for 2 years" (previously "up to 2 years") after the JCAR017 infusion, unless the subject it lost to follow-up and will then enter into a separate long-term follow up (LTFU) study

- Updated length of study enrollment from [redacted] to [redacted] months (Protocol Summary)
- Clarified that dose finding data from B-ALL subjects who have become MRD+ or MRD negative upon restaging prior to initiation of LD chemotherapy will be evaluable for the dose-limiting toxicity (DLT) analysis and be included in the identification of the RP2D in the Phase 1 (Protocol Summary, Section 1.3.2.1, Section 3.1.1, Section 9.2.3)
- Clarified that the Safety Review Committee (SRC) in Phase 1 will recommend a Phase 2 dose based on an integrated assessment of the safety, pharmacokinetics (PK) data and preliminary efficacy information from at least 10 pediatric subjects treated at the RP2D. Analysis of the JCAR017 manufactured product may also be considered (Protocol Summary, Section 3.1.1, Section 7.2.5.1, Section 9.1.1, Section 9.3.1, Section 9.7.1.1)
- Clarified JCAR017 treatment gating of subjects in Phase 1 and 2 (Protocol Summary, Section 1.3.2, Section 3.1.3)
- Clarified that the 10 pediatric subjects treated at the RP2D in Phase 1 will be included in, and form part of the sample size in Phase 2 (Cohort 1 and 2). The protocol therefore intends to treat 81 primary endpoint evaluable pediatric subjects in Phase 2, if warranted by the evaluation of results at the completion of the first stage of the study in each cohort (Protocol Summary, Section 3.1.2, Section 9.3.2)
- Clarified that Celgene may elect to explore the identified RP2D in up to 20 additional B-ALL subjects between 18 and 25 years of age in an optional cohort in Phase 2, if it is determined that the risk-benefit profile is such that exploration is warranted after consultation with the SRC (Protocol Summary, Section 1.3.2.2, Section 3.1.2)
- Part A (leukapheresis and JCAR017 product generation) and Part B (Treatment and Post Treatment Period), have been renamed to “Pre-treatment Period” and “Treatment and Post-treatment Follow-up Period”, respectively for clarity (change in terminology only) (Protocol Summary, Section 1.3.1, Table 2, Section 3.1.3, Section 3.4, Section 3.5 , Table of Events, Section 6.2, Section 6.2.2, Section 6.8, Section 8.2, Section 9.5, Section 9.7.2.2)
- Clarified that B-NHL subjects ≥ 18 years of age will not be eligible for this protocol (Protocol Summary)
- Clarified JCAR017 dosing will be capped at 100 kg for all dose levels (Protocol Summary, Section 1.3.3.1, Section 7.2.5.1)
- Clarified subjects, 18 to 25 years of age, will receive JCAR017 at the RP2D to be studied (previously a flat dose equivalent to 100 kg) (Protocol Summary, Section 1.3.3.1, Section 3.1.2, Section 7.2.5.2, Section 9.1.2, Section 9.3.2)
- Adverse Events of Special Interest (AESIs) were clarified and hypogammaglobulinemia, prolonged cytopenias and surveillance for second primary malignancies were added (Protocol Summary, Section 10.10)
- Updated the National Comprehensive Cancer Network (NCCN) response criteria guidelines for pediatric B-ALL to current version V1.2020 (Protocol Summary, Section 6.10.1, Appendix B)

- Incorporated an enrollment dropout rate of 18% into the study sample size justification; clarified that a total of 124 pediatric subjects may be enrolled to ensure that approximately up to 101 primary endpoint evaluable pediatric subjects (up to 30 subjects in Phase 1 and up to 71 additional subjects in Phase 2) are treated with JCAR017 (Protocol Summary, Section 3.1, Section 9.3)
- Updated the method to be used to determine the presence of the viral vector from quantitative polymerase chain reaction (qPCR) to droplet digital polymerase chain reaction (ddPCR) (Section 1.3.4, Section 6.11, Section 6.11.1)
- Clarified that JCAR017 pharmacokinetics will be assessed by ddPCR for secondary endpoint analysis [redacted] to characterize the expansion and persistence of JCAR017 CAR T-cell subsets (Table 2)
- Added a one-time retreatment with intra-patient dose-escalation for pediatric subjects at Dose Level 1 (DL1) who have not experienced severe toxicity and have no response on Day 28 after JCAR017 infusion (Section 1.3.3.1, Section 7.2.5.1.2)
- Clarification on the monitoring of vital signs (Table 3, Section 6.2.1.3, Section 7.2.4).
- Clarified that subject B-ALL enrollment in Phase 2 will be prioritized to Cohort 1 (r/r B-ALL) (Section 3.1.2)
- Added reference to Data Safety Monitoring Board (DSMB) and updated the frequency of DSMB meetings to occur approximately twice a year (from quarterly) throughout the trial and as needed to address any safety issues that may arise (Section 9.9.3)
- Clarified that the Karnofsky score will be used for subjects $\geq$ 16 years of age and Lansky score will be used for subjects < 16 years of age (Section 6.1.2, Section 6.2.1.2, Section 6.2.1.3, Section 6.1.4, Section 6.2.1.5, Section 6.2.1.7, Section 6.2.2, Section 6.3, and Section 6.9.7)
- Updated figures for Overall Study Design and Study Schematic (Figure 1 and Figure 2)
- Clarified that if the maximum serum creatinine based on age/gender for inclusion is not met, subjects with a radioisotope glomerular filtration rate (GFR) > 70 mL/min/1.73 m^2 are eligible (Section 4.2)
- Removed the requirement of two consecutive negative tests confirming absence of JCAR017 T cells (Section 4.2)
- Updated the definition of postmenopausal when determining childbearing potential and separated out highly effective and additional effective methods of contraception (Section 4.2, Table 3)
- Examples of low dose chemotherapy and oral anticancer agents were removed (Section 4.3, Section 6.1.3)
- Revised and clarified exclusion criteria of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 3 months of leukapheresis (Section 4.3)
- Added timepoints at leukapheresis and pre-treatment evaluation for Medical History to align with adverse event (AE) reporting requirements (Table 3)

- Removed requirement for subjects to perform pulmonary function test (FEV_1) (Table 3, Section 6.1.1)
- Clarified all evaluations, research sampling and laboratory assessments must be done prior to administration of LD chemotherapy or JCAR017 (Table 3)
- Clarified that the infectious disease marker blood sample (viral serology) performed at the leukapheresis visit is applicable to European sites only (Table 3)
- The Screening Period was updated to "up to 14 days" as all steps can be completed during this time, and for consistency with other JCAR017 studies (Table 3, Section 6.1.1)
- Extended time windows for assessments performed on Day 28 and Day 56 (Table 3)
- Removed urinalysis assessments (Table 3, Section 6.1.1, Section 6.2.1.3, Appendix D)
- Added research sampling timepoints for peripheral blood for JCAR017 PK [redacted] at LD chemotherapy visits, Day 1, 2, 4, 10 and 21 to support the Phase 1 dose finding (Table 3, Section 6.2.1.2, Section 6.2.1.3, Section 6.2.1.4, Section 6.2.1.6, Section 6.2.1.7)

[redacted]

- Clarified cerebrospinal fluid (CSF) assessment at screening are for subjects with suspected or confirmed CNS involvement; and subsequent assessments are only for subjects with confirmed CNS involvement. In addition, clarified CNS imaging should only be performed as clinically indicated. (Table 3, Section 6.1.4, Section 6.2.1.7, Section 6.2.2, Section 6.9.6)
- Clarified CSF assessments (post JCAR017 infusion) are not required for subjects in CR/CRi following JCAR017 administration, unless suspicion of CNS relapse (Table 3, Section 6.9.6)
- Added classification of CNS status, definition of CNS remission and CNS relapse (Section 6.9.6)
- Clarified that B-ALL subjects will be retrospectively reassigned to the appropriate cohort should their pre-LD chemotherapy disease status show a change from screening (Table 3, Section 6.1.4, Section 6.10.1)
- Added where applicable, institutional decision boards (eg, multidisciplinary tumor boards, Réunion de concertation pluridisciplinaire [RCP]) should be involved for subject selection (Section 6.1.1)
- Clarified donor chimerism and human leukocyte antigen (HLA) typing is not required to be repeated if results are available and performed within 3 months prior to screening (Table 3, Section 6.1.1)

- [redacted]
- [redacted]
- Clarified MRD will be assessed by a validated assay in bone marrow (BM) samples at a central "analytical" laboratory (Table 3, Section 6.1.1, Section 6.1.4, Section 6.10.1.1)
- Updated the name of the "[redacted] collection manual" to the "MNC collection manual" (Table 3, Section 6.1.2)
- Clarified that hematology at the leukapheresis visit includes a complete blood count (CBC) with differential within 24 hours prior to leukapheresis and must include absolute lymphocyte count (ALC) (Section 6.1.2)
- Added the washout periods prior to leukapheresis and prior to LD chemotherapy table (Table 4)
- Clarified anticancer treatment refers to "bridging chemotherapy" for disease control while JCAR017 is being manufactured (Protocol Summary, Section 3.1. 3, Section 6.1.3)
- Clarified subjects must continue to have confirmed disease, including measurable disease by computed tomography/magnetic resonance imaging (CT/MRI) for B-NHL subjects (Section 6.1.3)
- Clarified that all pretreatment evaluations must be performed within 7 days prior to LD chemotherapy regardless of whether the subject has had intervening anticancer therapy, unless otherwise noted (Section 6.1.4)
- For B-NHL subjects who did not receive intervening anticancer therapy, the time frame was updated from 6 weeks to 3 weeks prior to the start of LD chemotherapy for CT/MRI scans to be repeated at the Pre-treatment visit (Section 6.1.4)
- Clarified that subjects who demonstrate morphological remission and who are MRD negative upon restaging prior to initiation of LD chemotherapy will still be treated and followed on study but may be replaced for efficacy analysis (Section 6.1.4, Section 6.10.1.1, Section 9.2.4, Section 9.6.2.3)
- Clarified a delay of LD chemotherapy of more than 14 days requires discussion with Celgene and may require rescreening (Section 6.2.1.2)
- Clarified assessment of height is only done on first day of LD chemotherapy (Section 6.2.1.2)
- Added criteria subject must meet following JCAR017 infusion and prior to discharge from the hospital. In addition, subjects who do not have adequate social support (a full-time caregiver) outside of the hospital or do not have reliable transportation to the clinic for scheduled evaluations or emergencies post-therapy should be considered for hospitalization for the first 30 days (previously 14 days) following JCAR017 infusion. (Section 6.2.1.3)

- Clarified response evaluation is done be local Investigator review and Independent Review Committee (IRC) (Section 6.2.1.7, Section 6.2.2)
- Added clarification that subjects who receive hematopoietic stem cell transplantation (HSCT) post-JCAR017 (but no other subsequent anticancer treatment) should continue to undergo response/efficacy evaluations, unless they have demonstrated relapse/PD prior to HSCT (Section 6.2.2)
- Added [redacted] as an unscheduled assessment in the event a subject develops a second primary malignancy (Section 6.3, [redacted] Section 6.11.1)
- Added assessment of second primary malignancies to Post-Treatment Follow-up Period and Post-study follow up in LTFU protocol (Protocol Summary, Section 1.3.1)
- Added the "Second Primary Malignancies Follow-up Period" and language that if a subject develops a second primary malignancy, Celgene will request a tumor sample, BM and blood samples (Section 6.6, [redacted] and Section 6.11.1)
- Clarified that disease status will occur for at least 5 years in the separate LTFU protocol. In addition, details on all subsequent anti-neoplastic treatments for at least 5 years must be documented (Section 6.8)
- Added additional guidance for physical examination assessments (Section 6.9.1)
- Added literature reference to assess Tanner Staging and clarified that once Tanner Stage 5 is met, subsequent Tanner assessments do not need to be performed (Section 6.9.2)
- Combined pulse oximetry under vital signs (Section 6.9.3)
- [redacted]
- Added guidance for efficacy evaluation and required response assessments to be performed for B-ALL and B-NHL subjects (Section 6.10)
- Defined MRD relapse (Section 6.10.1.1)
- Clarified designation of response for the primary and "select secondary based" endpoints will be based on evaluations made by the IRC (Section 6.10.3)
- Clarified that results for IRC will not be provided to clinical sites (Section 6.10.3)
- Clarified that any observation of clonal outgrowth (clonal dominance), or monoclonality, will be reported as a serious adverse event (SAE) within 24 hours (Section 6.11.1)
- Clarifications made for [redacted] exploratory analysis (Table 1, Table 2, [redacted])
- "Subject Reported Outcomes" or "Health-related Quality of Life (HRQoL)" were both renamed to "Patient Reported Outcomes" for clarity (change in terminology only) (Table 1, Table 2, Table 3, Section 6.13)
- Clarified the age appropriate versions and provided guidance for administration of the pediatric quality of life (PedsQL) Patient Reported Outcomes (PRO) questionnaires; Parent/Caregiver Reported Outcomes was added to Table of Events; sample copies of all

PedsQL questionnaires were removed in the appendices (Table 3, Table 5, Section 6.13, Appendix G-J)

- Clarified JCAR017 paracetamol/acetaminophen premedication (Section 7.2.2, Section 8.3)
- Clarified that in case a subject cannot tolerate diphenhydramine hydrochloride (or it's not commercially available), an equivalent antihistamine may be substituted for JCAR017 premedication (Section 7.2.2, Section 8.3)
- [redacted]
- Updated list of medications that should be reported during inpatient and intensive care unit (ICU) stays (Section 8.1)
- Information regarding the reporting period and other details related to concomitant medications was moved to table format (Section 8.1)
- Clarified the definition of therapeutic doses of corticosteroids for pediatric subjects defined as > 0.4 mg/kg (maximum 20 mg/day prednisone) or equivalent (Section 4.3, Table 4, Section 8.2)
- Updated list of prohibited medications during treatment and follow-up periods (Section 8.2).
- Added reference to the currently approved cyclophosphamide and fludarabine phosphate Summary of Product Characteristics (SmPCs) (Section 8.3)
- Language was added for sites to have tocilizumab readily available prior to JCAR017 administration as required for treatment and management of cytokine release syndrome (CRS) (Section 8.3)
- Additional risk-group sub-analysis were added (Section 9.1)
- Modification of the definition of the Dose-limiting Toxicity Analysis Population (Section 9.2.3)
- Modification of the definition of the Efficacy Analysis Population (Section 9.2.4)
- Added the Patient Reported Outcome Analysis Population (Section 9.2.9)
- Clarified Phase 1 and Phase 2 primary and secondary endpoints (Protocol Summary, Section 9.6.1, Section 9.6.2)
- Clarified for the analysis of the HSCT rate, the time of proceeding to HSCT is defined as the time of commencing the conditioning regimen as required for HSCT (Section 9.6.2.7)
- Clarified the JCAR017 manufacturing feasibility secondary endpoint, defining successful and unsuccessful JCAR017 product generation (Section 9.9.1)
- Clarified that the SRC will include up to 5 active Investigators (Section 9.9.2)

- Independent Review Committee (previously Section 9.9.4) was moved under Efficacy (Section 6.10.3)
- Clarified the membership of the Scientific Steering Committee (Section 9.9.4)
- [redacted]
- Information regarding the reporting period and other details related to AE/SAEs was moved to table format (Section 10.1)
- Added guidance that, if available and adopted as per site standard practice, CRS and NT grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System (Lee, 2019) should also be recorded in the eCRF to inform future modifications of the management guidelines (Section 10.6.1)
- Revised the management of toxicities associated with JCAR017 for tumor lysis syndrome (TLS) and uncontrolled T-cell proliferation (Section 10.6.8, Section 10.6.11)
- Added events that are considered sufficient reasons for discontinuing a subject who undergoes leukapheresis but does not receive study treatment (ie, Pre-Treatment discontinuation) (Section 11.1)
- References were updated (Section 17)
- Table of abbreviations was updated (Appendix A)
- Footnotes added to clarify Cairo-Bishop grading system for TLS (Appendix E)
- JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurologic Toxicities updated to Version 2.0 (Appendix F)
- Misspellings, style and formatting

SUMMARY OF CHANGES

AMENDMENT NO. 1.0

A PHASE 1B/2, OPEN-LABEL, SINGLE ARM, MULTICOHORT, MULTICENTER TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF JCAR017 IN PEDIATRIC SUBJECTS WITH RELAPSED/REFRACTORY B-ALL AND B-NHL

INVESTIGATIONAL PRODUCT (IP):	**JCAR017**
PROTOCOL NUMBER:	**JCAR017-BCM-004**
ORIGINAL DATE:	**29 March 2018**
AMENDMENT No. 1.0 DATE:	**07January 2019**
EudraCT NUMBER:	**2018-001246-34**
IND NUMBER	**016506**

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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

1. JUSTIFICATION FOR AMENDMENT

Following a death (respiratory failure Grade 5) of a subject on 10 December 2018 in study JCAR017-BCM-001, a global Phase 1/2 study of JCAR017 in R/R third-line aggressive B-cell lymphoma, the program-wide, Data Safety Monitoring Board (DSMB) was convened on 14 December 2018 to review safety data on all subjects treated with JCAR017 across all studies with a ≥ third-line DLBCL patient population.

The DSMB members recommended continuation of the JCAR017 trials with modifications. The modifications are detailed in an Urgent Safety Measure (USM) to modify the inclusion and exclusion criteria.

Significant changes included in this amendment are summarized below:

- **B-NHL subjects with vascular tumor invasion will not be eligible**

  Following the subject's death and review of the data, the DSMB recommended exclusion of B-NHL subjects with vascular tumor invasion. The following exclusion criteria was therefore added:

  "Tumor invasion of venous or arterial vessels (B-NHL subjects only)"

  Revised Sections: Section 4.3, Exclusion Criteria #17

- **Subjects with deep venous thrombosis (DVT) and/or pulmonary embolism (PE) will not be eligible**

  As additional measure, subjects with deep venous thrombosis (DVT) and/or pulmonary embolism (PE) will not be eligible. The following exclusion criteria was therefore added:

  "Deep Venous Thrombosis (DVT)/Pulmonary Embolism (PE) within 3 months of ICF signature and/or DVT/PE that requires ongoing therapeutic levels of anti-coagulation."

  Revised Sections: Section 4.3, Exclusion Criteria #18

The amendment also includes several other minor clarifications and corrections:

- Update Celgene Medical Monitor's contact information
- Misspellings, style and formatting
- Added potential risks associated with cytopenias and infections (Section 10.6.1).