CLINICAL STUDY PROTOCOL CRSP-ONC-001

A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Efficacy of Anti-CD19 Allogeneic CRISPR-Cas9–Engineered T Cells (CTX110) in Subjects With Relapsed or Refractory B Cell Malignancies

Study Drug: CTX110
Study Phase: 1/2
EudraCT: 2018-003916-38
IND: 18903
Date of Original Protocol: 06 February 2019
Date of Protocol Amendment: 12 September 2022, Amendment 6
Version: 7.0

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PROTOCOL SYNOPSIS

Sponsor: CRISPR Therapeutics AG	**Protocol Number**: CRSP-ONC-001
Name of Investigational Product: CTX110	**Phase of Development**: 1/2
Protocol Title: A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Efficacy of Anti-CD19 Allogeneic CRISPR-Cas9–Engineered T Cells (CTX110) in Subjects With Relapsed or Refractory B Cell Malignancies	
Number of Subjects Phase 1 Part A (dose escalation): Approximately 100 Phase 1 Part B (cohort expansion): Up to 30 Phase 2: Approximately 97	
Investigators: Multicenter	**Study Type**: Interventional
Investigational Product Description: CTX110 is a CD19-directed chimeric antigen receptor (CAR) T cell immunotherapy comprised of allogeneic T cells that are genetically modified ex vivo using CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats/ CRISPR-associated protein 9) gene editing components (single-guide RNA and Cas9 nuclease). The modifications include targeted disruption of the T cell receptor (TCR) alpha constant and beta-2 microglobulin (B2M) loci, and the insertion of an anti-CD19 CAR transgene into the TRAC locus via an adeno-associated virus expression cassette. The CAR is composed of an anti-CD19 single-chain variable fragment derived from murine antibody clone FMC63, a previously characterized anti-CD19 monoclonal antibody, the CD8 transmembrane domain, a CD28 costimulatory domain, and a CD3ζ signaling domain.	
Study Population: Phase 1 (dose escalation and cohort expansion) will be performed in adult subjects with B cell malignancies. In Phase 1, subjects will be assigned to independent dose escalation groups based on disease histology. Cohorts A, B, and C will enroll adult subjects with select subtypes of non-Hodgkin lymphoma (NHL), including diffuse large B cell lymphoma (DLBCL) not otherwise specified (NOS), high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, transformed follicular lymphoma (FL), grade 3b FL, and primary mediastinal B cell lymphoma (PMBCL). Cohort D will include adults with relapsed or refractory B cell acute lymphoblastic leukemia (ALL). Phase 1 (Dose escalation and cohort expansion) in the B cell ALL study population (Cohort D) will be conducted separately from the adult NHL study population (Cohorts A, B, and C). Phase 2 will be performed in adult subjects with select subtypes of NHL.	

Duration of Subject Participation: Subjects will participate in this study for up to 5 years after the last CTX110 infusion. After completion of this study, all subjects will be asked to participate in a separate long-term follow-up study for an additional 10 years to assess safety and survival.

Study Rationale: CAR T cell therapies are adoptive T cell therapeutics used to treat human malignancies. Although CAR T cell therapy has led to tremendous clinical success, including durable remission in relapsed/refractory NHL and ALL patients, the approved products are autologous and require patient-specific cell collection and manufacturing. Because of this, some patients have experienced disease progression or death while awaiting treatment. An allogeneic off-the-shelf CAR T cell product could provide benefits such as immediate availability, lack of manufacturing failures, and chemotherapy-naïve T cells providing a more consistent product relative to autologous CAR T cell therapies. Numerous approaches have been described to create allogeneic CAR T cell therapies. With CRISPR-Cas9 editing, disruption of the endogenous TCR and major histocompatibility complex (MHC) class I proteins can be achieved. TCR knockout should significantly reduce or eliminate the risk of graft vs host disease (GvHD), whereas MHC knockout could increase CAR T cell persistence. This first-in-human trial in subjects with relapsed or refractory B cell malignancies aims to evaluate the safety as well as efficacy of this CRISPR-Cas9–modified allogeneic CAR T cell approach.

Objectives

Phase 1

Primary objective, Part A (dose escalation): To assess the safety of escalating doses of CTX110 in combination with various lymphodepletion (LD) agents in subjects with relapsed or refractory B cell malignancies to determine the recommended Part B or Phase 2 dose and cohort

Primary objective, Part B (cohort expansion): To assess the preliminary efficacy of CTX110 in subjects with relapsed or refractory B cell malignancies, as measured by objective response rate (ORR)

Secondary objectives (dose escalation and cohort expansion):

- To further characterize the efficacy, safety, and pharmacokinetics (PK) of CTX110
- To evaluate the changes over time in patient-reported outcomes (PROs) associated with CTX110

Exploratory objectives (dose escalation and cohort expansion): [redacted]

Phase 2

Primary objective: To assess the efficacy of CTX110 in subjects with select NHL subtypes, as measured by objective response rate (ORR)

Secondary objectives:

- To further characterize the efficacy, safety, and pharmacokinetics (PK) of CTX110

- To evaluate the changes over time in patient-reported outcomes (PROs) associated with CTX110

Exploratory objectives: [redacted]

Study Design: This is an open-label, multicenter, Phase 1/2 study evaluating the safety and efficacy of CTX110 in subjects with relapsed or refractory B cell malignancies.

Phase 1

Phase 1 of the study will be divided into 2 parts: dose escalation (Part A) followed by cohort expansion (Part B).

During both Part A and Part B, the study will consist of 3 main stages as follows:

Stage 1: Screening to determine eligibility for treatment (1-2 weeks)

Stage 2: Treatment (**Stage 2A** and **Stage 2B**); see Table S1 below for treatment by cohort

Stage 3: Follow-up for all cohorts (up to 5 years after the last CTX110 infusion)

Phase 1 Part A (Dose Escalation)

Dose escalation (Part A) will investigate escalating doses of CTX110 and different LD regimens using a 3+3 design in approximately 100 subjects in 4 independent cohorts: Cohorts A, B, C, and D. These cohorts will allow preliminary evaluation of the safety, efficacy, and PK of CTX110 when used with different LD regimens, with or without additional CTX110 infusions, and in different B cell malignancies (i.e., NHL and adult B cell ALL), and different prior autologous CAR T cell therapy exposure, as summarized in Table S1 below.

After a dose level has been cleared, the sponsor, in consultation with the study safety review committee (SRC), may decide to enroll additional subjects at a given dose level. In any dose escalation cohort or subcohort, 6 additional subjects (up to 12 total subjects) may receive study treatment at or below the highest cleared dose level. Further, with SRC approval, 12 additional subjects (24 total) may receive study treatment in any one cohort or subcohort (A, B, C1, C2, D1, or D2) at or below the highest cleared dose level to gather additional safety information prior to cohort expansion.

For subjects who receive additional infusions of CTX110 based on disease response criteria and eligibility, as described in the protocol and in Table S1 below, the dose level for the additional CTX110 infusion will be at or below the highest CTX110 dose that has been cleared by the SRC and the sponsor with the planned LD regimen. Dose escalation rules and staggering will apply to all cohorts.

Table S1: Lymphodepletion Regimen and CTX110 Infusion Schedule (Part A Dose Cohorts)

Cohort	Disease Subtype	First Course of Treatment
A	NHL: Adult subjects with DLBCL NOS, high-grade B cell lymphoma with *MYC*	**Stage 2A** LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + **cyclophosphamide 500 mg/m^2** IV daily for 3 days; both agents

	and *BCL2* and/or *BCL6* rearrangements, grade 3b FL, transformed FL, or PMBCL	should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion. **Stage 2B** • Initial CTX110 infusion on Day 1 starting at DL1 • A second infusion of CTX110 on Day 35 (-7 days/+21 days) administered with LD chemotherapy for subjects who achieve SD or better at Day 28 scan (based on Lugano criteria).
B*	Same as Cohort A, with additional inclusion criteria related to prior autologous CAR T cell therapy	**Stage 2A** LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + **cyclophosphamide 750 mg/m^2** IV daily for 3 days; both agents should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion. **Stage 2B** • Initial CTX110 infusion on Day 1 starting at DL4 • A second infusion of CTX110 on Day 35 (-7 days/+21 days) with LD chemotherapy (co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days) to subjects who achieve SD or better at Day 28 scan (based on Lugano criteria).
C (Subcohorts C1 and C2)	Same as Cohort A	**Stage 2A** LD regimen: Daratumumab + LD chemotherapy Daratumumab administration: One dose of daratumumab[1] 16 mg/kg by IV infusion or 1800 mg by SC injection ≥1 day prior to starting LD chemotherapy and within 10 days prior to CTX110 infusion. To facilitate administration, the first 16 mg/kg IV dose may be split (to 8 mg/kg) over 2 consecutive days. LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + **cyclophosphamide 500 mg/m^2** IV daily for 3 days; both agents should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion. **Stage 2B** <u>Cohort C1</u> • Initial CTX110 infusion on Day 1 starting at DL3 • No second infusion of CTX110 on Day 35 • For subjects who achieve SD or better on Day 28, 2 additional doses of daratumumab (16 mg/kg by IV infusion or 1800 mg by SC injection) will be administered at Day 28 (± 4 days) and Month 2 (± 4 days) visits. <u>Cohort C2</u> • Initial CTX110 infusion on Day 1 starting at or below the DL cleared in Cohort C1 • A second infusion of CTX110 on Day 35 (-7 days/+21 days) administered with daratumumab[2] and LD chemotherapy to subjects who achieve SD or better at Day 28 scan (based on Lugano criteria).

D (Subcohorts D1 and D2)	Adult B cell ALL D1: BM involvement with ≥5% blasts. D2: BM <5% blasts and MRD-positive (>1 × 10^{-4} cells detected by flow cytometry or PCR or NGS including ClonoSEQ or positive BCR-ABL transcript for Ph+ disease).	**Stage 2A** LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + **cyclophosphamide 500 mg/m^2** IV daily for 3 days; both agents should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion.[3] **Stage 2B** Cohort D1 (BM involvement with ≥5% blasts) • Initial CTX110 infusion on Day 1 starting at DL2 or DL3 • A second infusion of CTX110 on Day 35 (-7 days/+21 days) with LD chemotherapy if subject has a decrease in BM blast count at Day 28 of ≥50% but blast count remains ≥5% or is MRD-positive. Cohort D2 (BM involvement with <5% blasts and MRD-positive) • CTX110 infusion on Day 1 starting at or below the DL cleared in D1 • Second infusion of CTX110 on Day 35 for subjects who have demonstrated a reduction in detectable MRD and remain MRD positive.

ALL: acute lymphoblastic leukemia; BM: bone marrow; CAR: chimeric antigen receptor; DL: Dose Level; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; IV: intravenous(ly); LD: lymphodepleting; MRD: minimal residual disease; NGS: next-generation sequencing; NHL: Non-Hodgkin Lymphoma; NOS: not otherwise specified; PCR: polymerase chain reaction; PMBCL: primary mediastinal large B cell lymphoma; SC: subcutaneous; SD: stable disease.

Note: Subjects in legacy Cohort F (discontinued in Version 6.0 of the protocol) have been merged with Cohort A.

Note: Subjects should meet the criteria specified in the protocol prior to both the initiation of LD chemotherapy and infusion of CTX110 and should meet criteria specified for second or subsequent infusions prior to receiving any additional doses of CTX110. Criteria for LD chemotherapy should be confirmed prior to infusion of daratumumab as applicable. The CTX110 infusion on Day 35 (-7 days/+21 days), if applicable, may be administered without LD chemotherapy if subject is experiencing significant cytopenias (see protocol for details).

Subjects in all cohorts have the option to receive an additional infusion of CTX110 with LD chemotherapy (co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days) after PD, if subjects had response after prior infusion. Additional infusion after PD must be within 18 months of the initial CTX110 infusion and ≥4 weeks after last infusion.

* Cohort B will enroll subjects only at selected investigative sites, at the sponsor's discretion.

[1] Daratumumab may be administered as an SC injection (1800 mg/30,000 units of hyaluronidase-fihj) or as an IV infusion of 16 mg/kg, per local prescribing information.

[2] For subjects in Cohort C2 who respond to treatment (i.e., achieve SD or better on Day 28), an additional dose of daratumumab will be administered at the Day 28 visit and an additional infusion of CTX110 will be administered on Day 35. A second additional daratumumab dose will be administered as part of the LD regimen for Day 35 unless within 14 days of the previous Day 28 dose.

[3] In Cohort D, additional subjects may be enrolled to explore alternative LD dose regimen in which cyclophosphamide may be administered at a dose of 750 mg/m^2 IV daily for 3 days, starting at a CTX110 dose level at or below the highest dose level that has been cleared with LD dose containing 500 mg/m^2 IV daily for 3 days and if it has been agreed by the SRC and the sponsor. Additional subjects enrolled will follow dose escalation rules as described in the protocol. In that instance, for the second infusion on Day 35 (where applicable), the cyclophosphamide dose in LD chemotherapy will be 500 mg/m^2.

Cohorts A, B, and C will comprise subjects with NHL, including DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, transformed FL, grade 3b FL, and PMBCL. Cohort D will consist of subjects with B cell ALL. Enrollment and allocation of subjects

to each cohort will be at the sponsor's discretion. In the dose escalation part of the study, CTX110 infusion in Cohorts B, C, and D will begin at dose levels specified in Table S1 above after assessment and confirmation of safety by the study SRC and sponsor. Subjects with B cell ALL will be exclusively assigned to Cohort D in parallel with other cohorts.

Phase 1 Part B (Cohort Expansion)

Cohort expansion (Part B) will begin with Cohort A to further evaluate the safety and efficacy of CTX110 in NHL subjects. The sponsor, in agreement with the SRC and an independent data safety monitor board (DSMB), has selected 6×10^8 CAR^+ T cells (DL4) as the recommended Part B dose for cohort expansion, with an initial CTX110 infusion on Day 1 at DL4 and, for subjects who achieve SD or better at Day 28 scan (based on Lugano criteria), a second infusion at DL4 on Day 35 (-7 days/+21 days), both administered with LD chemotherapy. Cohort expansion (Part B) can be performed for any of the NHL or adult B cell ALL cohorts that have completed the dose escalation part and have determined the Part B dose and regimen per the protocol-specified criteria.

Initially, up to 30 subjects with NHL will be enrolled in Part B. The first NHL cohort to be expanded may be followed by the expansion of other NHL or adult B cell ALL cohorts, as those complete the dose escalation part of the study, with agreement from the SRC, independent DSMB, and at the sponsor's discretion. If other cohorts expand, the sample size estimation for the first cohort expansion will also apply to the subsequent cohort expansion, thus increasing the total number of enrolled subjects in Part B. Where required, regulatory approval will be obtained prior to enrolling any subjects from that region into any cohort expansion.

Dose escalation for other cohorts may continue in parallel to cohort expansion or Phase 2 enrollment. Dose escalation for subjects with adult B cell ALL is anticipated to continue in parallel to cohort expansion and Phase 2 enrollment for NHL cohorts.

Phase 2

Following dose escalation of any Phase 1 cohort, the sponsor may begin enrollment in Phase 2 to evaluate efficacy and safety of CTX110 in a larger population of subjects. Enrollment to Phase 2 will be at the sponsor's discretion, with agreement from the SRC and DSMB.

Phase 2 will begin with subjects with NHL at the recommended Part B dose and regimen for Phase 1 Cohort A, to further evaluate the efficacy and safety of CTX110 in subjects with NHL. Approximately 97 subjects with NHL will be enrolled. Where required, regulatory approval will be obtained prior to enrolling any subjects from that region into Phase 2.

Phase 2 may be conducted in parallel with Phase 1 dose escalation or cohort expansion of other cohorts in the study.

Considerations for Phase 1 and Phase 2

For Phase 1 Part A (dose escalation), subjects must remain within proximity of the investigative site (i.e., 1-hour transit time) for 28 days after each CTX110 infusion. For Phase 1 Part B (cohort expansion) and Phase 2, subjects must remain within proximity of the investigative site (i.e., 1-hour transit time) for 28 days after the first CTX110 infusion and at least 14 days for subsequent CTX110 infusions, or longer if justified by subject's clinical status or as required by local regulation or site practice. During this acute toxicity monitoring period, subjects will be routinely

assessed for adverse events (AEs), including cytokine release syndrome (CRS), neurotoxicity, and GvHD. Toxicity management guidelines are provided in the study protocol. During Phase 1 dose escalation, all subjects will be hospitalized for the first 7 days following each CTX110 infusion, or longer if required by local regulation or site practice.

After the acute toxicity monitoring period, subjects will be subsequently followed for up to 5 years after the last CTX110 infusion with physical exams, regular laboratory and imaging assessments, and AE evaluations. After completion of this study, subjects will be asked to participate in a separate long-term follow-up study for an additional 10 years to assess long-term safety and survival.

For all cohorts, LD chemotherapy (or the first daratumumab dose for subjects in Phase 1 Cohort C) will be delayed if any of the following signs or symptoms are present:

- Significant worsening of clinical status that, according to the investigator, increases the potential risk of AEs associated with LD chemotherapy
- Requirement for supplemental oxygen to maintain a saturation level of >91%
- New uncontrolled cardiac arrhythmia
- Hypotension requiring vasopressor support
- Active infection: Positive blood cultures for bacteria, fungus, or virus not responding to treatment, or negative culture but active infection based on investigator judgment in consultation with the medical monitor
- Grade ≥2 acute neurological toxicity
- Unresolved infusion reaction due to daratumumab treatment (Phase 1 Cohort C only)

Additional criteria for LD chemotherapy prior to subsequent CTX110 infusions after Day 1 are further specified in the protocol.

For all cohorts, each CTX110 infusion will be delayed if any of the following signs or symptoms are present:

- New active uncontrolled infection
- Worsening of clinical status compared to prior to start of LD chemotherapy that, in the opinion of the investigator, places the subject at increased risk of toxicity
- Grade ≥2 acute neurological toxicity

Additional Day 35 infusion specific criteria are described in the respective section of the protocol.

Dose escalation will be performed using a standard 3+3 design in which 3 to 6 subjects will be enrolled at each dose level depending on the occurrence of dose-limiting toxicity (DLT), as defined in the protocol. The SRC will review available data when the DLT observation period ends for the last subject enrolled in each cohort. The SRC will be responsible for making dose escalation decisions based on review of all available safety and PK data. Throughout dose escalation, for cases in which a dose had been cleared in a cohort or subcohort (e.g., Subcohort D1) and dose escalation is permitted, the sponsor in consultation with the SRC may alternatively decide to enroll an additional number of subjects for a total of up to 24 at the current

dose level to gather additional safety data. Based on ongoing assessment of benefit and risk, the SRC may stop dose escalation before a maximum tolerated dose (MTD) is determined.

Dose Levels and Dose Limiting Toxicities for Phase 1 Part A (Dose Escalation)

The following doses of CTX110, based on the total number of CAR^+ T cells, may be evaluated in this study. The starting dose for escalation will be selected separately for each cohort and will reflect the cumulative safety data across all cohorts for each study population (NHL, adult B cell ALL). Whenever escalation begins in a new cohort, the sponsor and SRC will discuss and agree on the starting dose level, which will not exceed the highest dose level cleared in Cohort A. There will be a dose limit of [redacted] TCR^+ cells/kg for all dose levels, which will determine the minimum weight for dosing.

Table S2: Dose Escalation of CTX110

Dose Level	Total CAR^+ T Cell Dose
−1	1×10^7
1	3×10^7
2	1×10^8
3	3×10^8
3.5*	4.5×10^8
4	6×10^8
5**	9×10^8

CAR: chimeric antigen receptor; DL: Dose Level.
* DL3.5 is an optional de-escalation dose level.
**Note: The sponsor, with approval of the safety review committee, may explore DL5 (9×10^8 CAR^+ T cells) in parallel to cohort expansion.

The DLT evaluation period will begin with the initial CTX110 infusion and last for 28 days.

Subjects who receive a subsequent CTX110 infusion on Day 35 and/or after disease progression, or who receive Day 28 and Month 2 doses of daratumumab (Cohort C1) will be monitored for frequency and severity of AEs and adverse events of special interest during the immediate 28-day period after each additional CTX110 infusion or, for Cohort C1, after additional doses of daratumumab in addition to the assessment of safety per the DLT criteria defined in the protocol.

For Cohort A: In Dose Level (DL) 1 (and DL-1, if required), subjects will be treated in a staggered manner such that the second and third subjects will only receive CTX110 after the previous subject has completed the DLT evaluation period. In subsequent dose levels or for additional subjects enrolled at the same dose level, cohorts of up to 3 subjects may be enrolled and dosed concurrently.

For Cohorts B, C, and D: The first 2 subjects within each cohort will be treated in a staggered manner at the starting dose level and at each subsequent DL, such that the second subject will only receive CTX110 after the previous subject has completed the DLT evaluation period. For

additional subjects enrolled at the same dose level, cohorts of up to 3 subjects may be enrolled and dosed concurrently.

For Cohort D, the first 2 subjects at each dose level of Subcohort D1 (adult B cell ALL subjects with ≥5% blasts) will be treated in a staggered manner such that the second subject will only receive CTX110 after the previous subject has completed the DLT evaluation period. In Subcohort D2 (adult B cell ALL subjects with <5% blasts and MRD positive), up to 3 subjects may be enrolled and dosed concurrently if the dose level has been cleared by the SRC in Subcohort D1. The opposite will not be allowed: if 3 subjects in Subcohort D2 are cleared, then Subcohort D2 alone will advance to the next dose level.

Subjects must receive CTX110 to be evaluated for DLT. If a subject discontinues the study any time prior to the initial CTX110 infusion, the subject will not be evaluated for DLT and a replacement subject will be enrolled at the same dose level as the discontinued subject. If a DLT-evaluable subject has signs or symptoms of a potential DLT, the DLT evaluation period will be extended according to the protocol-defined window to allow for improvement or resolution before a DLT is declared.

Toxicities will be graded and documented according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, except for CRS (ASTCT criteria), neurotoxicity (ICANS criteria and CTCAE v5.0), and GvHD (Mount Sinai Acute GVHD International Consortium criteria).

A DLT will be defined as any of the following events occurring during the DLT evaluation period that persists beyond the specified duration (relative to the time of onset):

- Grade ≥2 GvHD that is steroid-refractory (e.g., progression of disease [PD] after 3 days of steroid treatment [e.g., 1 mg/kg/day], stable disease [SD] after 7 days, or partial response [PR] after 14 days of treatment)
- Death during the DLT period (except due to PD)
- Grade 4 neurotoxicity of any duration that is related or possibly related to CTX110
- Any CTX110-related grade 3 or 4 toxicity that is clinically significant according to the investigator's judgment and does not improve within 72 hours

  The following will **NOT** be considered as DLTs:

  – Grade 3 or 4 CRS that improves to grade ≤2 within 72 hours
  – Grade 3 neurotoxicity (e.g., encephalopathy, confusion) that improves to grade ≤2 within 14 days
  – Grade 3 or 4 fever
  – Bleeding in the setting of thrombocytopenia (platelet count <50 $\times 10^9$/L); documented bacterial infections or fever in the setting of neutropenia (absolute neutrophil count <1000/mm^3)
  – Hypogammaglobulinemia

- Grade 3 or 4 pulmonary toxicity that resolves to grade ≤2 within 7 days. For subjects intubated due to fluid overload from supportive care, this may be extended to 14 days.
- Grade 3 or 4 liver function studies that improve to grade ≤2 within 14 days
- Grade 3 or 4 renal insufficiency that improves to grade ≤2 within 21 days
- Grade 3 or 4 thrombocytopenia, neutropenia, anemia, or lymphopenia will be assessed retrospectively. After at least 6 subjects are infused, if ≥50% of subjects have prolonged cytopenias (i.e., lasting more than 28 days post infusion), dose escalation will be suspended pending SRC assessment. For Cohort D: grade ≥3 cytopenias that were present at the start of LD chemotherapy may not be considered a DLT pending SRC review and identification of another etiology.

AEs that have no plausible causal relationship with CTX110 will not be considered DLTs.

Study Oversight

A study SRC consisting of investigators and sponsor representatives will review all available safety data and make decisions regarding dose escalation (or de-escalation), additional CTX110 infusion, LD chemotherapy dose regimen, and daratumumab (Darzalex®, Janssen) dose regimen to determine the recommended Phase 1 Part B dose and regimen for cohort expansion or the recommended Phase 2 dose and regimen. The SRC may also propose revisions to the DLT definitions and dosing schema during dose escalation. The SRC will continue to meet regularly during the expansion parts of the trial to discuss toxicity management algorithms and review of individual subject cases.

An independent DSMB consisting of at least 2 physicians and 1 statistician with appropriate scientific and medical expertise will review expedited reports of any serious adverse events (SAEs), including expedited SAEs, SAEs resulting in death, and aggregate safety data twice a year. The DSMB will also review the interim analysis in Phase 2.

Study Eligibility

Inclusion Criteria

For all cohorts, unless otherwise specified.

1. Age ≥18 years (Phase 1 Cohorts A, B, and C and Phase 2), or ≥18 to ≤70 years (Phase 1 Cohort D)
2. Able to understand and comply with protocol-required study procedures and voluntarily sign a written informed consent document
3. Diagnosed with 1 of the following B cell malignancies:

   Phase 1 Cohorts A, B, and C (C1 and C2) and Phase 2: Histologically confirmed B cell NHLs: DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, transformed FL, grade 3b FL, or PMBCL

   - Confirmation of tumor histology from local pathology lab (archival tissue from last relapse/progression [within 3 months of enrollment] or biopsy during screening [or

within 28 days prior to CTX110 infusion, if a recent sample was collected as part of standard of care])

- At least 1 measurable lesion that is fluorodeoxyglucose positron emission tomography (PET)–positive, as defined by Lugano criteria (Deauville score of 4 or 5 on Lugano criteria 5-point scale). Note: Previously irradiated lesions will be considered measurable only if progression is documented following completion of radiation therapy.

Phase 1 Cohort D: Histologically confirmed B cell ALL

- Subcohort D1: Bone marrow involvement with ≥5% blasts (see investigational plan in the protocol body)
- Subcohort D2: Bone marrow minimal residual disease (MRD)–positive (defined as $>1 \times 10^{-4}$ cells detected by flow cytometry or polymerase chain reaction [PCR] or next-generation sequencing [NGS] including ClonoSeq or positive BCR-ABL transcript for Ph+ disease) in subjects with bone marrow with ≤5% blasts. Subjects in Subcohort D2 may be enrolled with local baseline MRD results pending, as long as qualifying results within 3 months of enrollment are available.

4. Refractory or relapsed disease, as evidenced by the following cohort-specific criteria:

   Phase 1 Cohorts A, B, and C (NHL) and Phase 2 (NHL): 2 or more prior therapies, including an anti-CD20 monoclonal antibody and an anthracycline-containing regimen. Subjects who have received [redacted] must have recovered from HSCT-related toxicities.

   - Refractory disease is defined as subjects with PD on last therapy, or SD following at least 2 cycles of therapy.
   - For subjects with transformed FL, subjects must have received at least 1 line of chemotherapy for disease after transformation to DLBCL.
   - For **Phase 1 Cohort B**, subjects must meet the following criteria:
     - Received prior treatment with an approved autologous CD19-directed CAR T cell therapy (e.g., axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) ≥12 months prior to enrollment
     - Achieved a CR for ≥4 months duration from prior treatment with autologous CD19-directed CAR T cell therapy
     - No grade ≥ 2 ICANS from prior CAR T cell therapy
     - No history of grade 4 CRS
     - No other prior or residual toxicity from prior CAR T cell therapy that, in the investigator's judgement, would place subject at increased risk of toxicity from a subsequent CAR T cell therapy
     - Age <70 years old
     - No elevated lactate dehydrogenase (LDH) (per institutional normal range)

Note: Subjects with relapse after autologous CAR T cell therapy <6 months and/or 6 to 12 months prior to enrollment, those with elevated LDH, and those >70 years old may be considered after SRC review of safety and efficacy data from at least 6 subjects in Cohort B.

Phase 1 Cohort D (adult B cell ALL):

- 2 or more prior therapies, or
- Any bone marrow relapse after allogeneic HSCT; or
- Philadelphia chromosome–positive if subjects are intolerant to or ineligible for tyrosine kinase inhibitor (TKI) therapy or have progressed after at least 1 line of TKI therapy.

5. Eastern Cooperative Oncology Group performance status 0 or 1
6. Meets criteria to undergo LD chemotherapy (all Phase 1 cohorts and Phase 2), CAR T cell infusion (all Phase 1 cohorts and Phase 2), and daratumumab administration (Phase 1 Cohort C only)
7. Adequate organ function:
   - Renal: Estimated glomerular filtration rate >50 mL/min/1.73 m^2
   - Liver: Aspartate transaminase or alanine transaminase <3 × upper limit of normal (ULN); total bilirubin <1.5 × ULN (for subjects with Gilbert's syndrome, total bilirubin <2 mg/dL)
   - Cardiac: Hemodynamically stable and left ventricular ejection fraction ≥45% by echocardiogram
   - Pulmonary: Oxygen saturation level on room air >91% per pulse oximetry
8. Female subjects of childbearing potential (postmenarcheal with an intact uterus and at least 1 ovary, who are less than 1 year postmenopausal) must agree to use acceptable method(s) of contraception from enrollment through at least 12 months after the most recent CTX110 infusion.
9. Male subjects must agree to use effective acceptable method(s) of contraception as specified in the protocol from enrollment through at least 12 months after the most recent CTX110 infusion.

Phase 1 Exclusion Criteria

For all cohorts, unless otherwise specified.

1. Treatment with the following therapies as described below:
   - Prior treatment with any gene therapy or genetically modified cell therapy, including CAR T cells. Exception: Phase 1 Cohort B will enroll subjects who received prior treatment with an approved autologous CD19-directed CAR T cell therapy.
   - Prior treatment with a CD19-directed therapy (e.g., CD19-directed antibody, bispecific T cell engager, or antibody-drug conjugate), unless there is confirmed CD19

expression (by immunohistochemistry or flow cytometry) after progression or relapse following most recent CD19-directed treatment. The requirement to confirm CD19 expression is optional in Phase 1 Subcohort D2. Subjects in Phase 1 Cohort B should demonstrate confirmed CD19 expression.

2. Prior allogeneic HSCT. Exception: For subjects with B cell ALL (Phase 1 Cohort D), prior allogeneic HSCT is permissible if it has been more than 6 months from HSCT at the time of enrollment; there is no evidence of acute or chronic GvHD; and the subject has recovered from HSCT-related toxicities, has been off immunosuppressive therapies for at least 3 months prior to enrollment, and has not received donor lymphocyte infusion for at least 2 months prior to enrollment.
3. Diagnosis of Burkitt's lymphoma/leukemia
4. Known contraindication to daratumumab (Phase 1 Cohort C only), cyclophosphamide, fludarabine, or any of the excipients of CTX110 product
5. Prior CNS disease
   - For NHL subjects: Detectable malignant cells from cerebrospinal fluid (CSF) or magnetic resonance imaging (MRI) indicating brain metastases during screening, or a history of central nervous system (CNS) involvement by malignancy (CSF or imaging).
   - For B cell ALL subjects: a prior history of CNS involvement with no evidence of current CNS disease during screening and/or those with CNS-2 disease, which is defined as the presence of blast cells in CSF containing <5 white blood cells/μL per National Comprehensive Cancer Network (NCCN) guidelines V2.2021 (NCCN, 2021), without neurological symptoms are eligible for the study. The SRC will review the first 2 subjects with CNS-2 ALL to allow additional subjects with CNS disease to be enrolled.
6. History of a seizure disorder, major cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
7. Unstable angina, clinically significant arrhythmia, or myocardial infarction within 6 months of enrollment, or grade 3 or higher pericardial effusion at the time of enrollment.
8. Presence of active bacterial, viral, or fungal infection that is uncontrolled, based on investigator judgment in consultation with the medical monitor
9. Positive for presence of human immunodeficiency virus (HIV) type 1 or 2, or active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Subjects with prior history of HBV or HCV infection who have documented undetectable viral load (by quantitative PCR or nucleic acid testing) are permitted. Infectious disease testing (HIV-1, HIV-2, HCV antibody and PCR, HBV surface antigen, HBV surface antibody, HBV core antibody) performed within 45 days of enrollment may be considered for subject eligibility
10. Previous or concurrent malignancy, except basal cell or squamous cell skin carcinoma, adequately resected and in situ carcinoma of cervix, or a previous malignancy that was completely resected and has been in remission for ≥5 years of enrollment

11. Radiation therapy within 14 days of enrollment
12. For Phase 1 Cohorts A, B, and C (NHL) and Phase 2 (NHL): Use of systemic antitumor therapy or investigational agent within 14 days or 5 half-lives, whichever is longer, of CTX110 infusion. Exceptions: 1) prior inhibitory/stimulatory immune checkpoint molecule therapy, which is prohibited within 3 half-lives of CTX110 infusion; and 2) rituximab, other anti-CD20 monoclonal antibodies, or polatuzumab vedotin use within 30 days prior to CTX110 infusion is prohibited (however PET/computed tomography scan needs to occur at least 2 weeks after last dose).

    For Phase 1 Cohort D (adult B cell ALL): Use of systemic antitumor therapy within 7 days of CTX110 infusion. Exceptions: 1) immunotherapy agents (i.e., rituximab, inotuzumab) must be stopped at least 14 days prior to CTX110 infusion; 2) long-acting chemotherapy agents (e.g., pegylated asparaginase, methotrexate >25 mg/m^2) must be stopped at least 14 days prior to CTX110 infusion; 3) Hydroxyurea must be stopped ≥72 hours before CTX110 infusion; and 4) investigational agent(s) must be stopped after 5 half-lives have passed before CTX110 infusion. Subjects must have recovered to grade 1 CTCAE from acute toxicity (except hematological) of all previous therapy prior to CTX110 infusion. 5) Steroids are permitted until the day before starting LD chemotherapy for maintenance or to allow for control of peripheral blood blasts.
13. Primary immunodeficiency disorder or active autoimmune disease requiring steroids and/or other immunosuppressive therapy
14. Diagnosis of significant psychiatric disorder or other medical condition that, in the opinion of the investigator, could impede the subject's ability to participate in the study
15. Women who are pregnant or breastfeeding
16. Life expectancy of less than 6 weeks
17. For Phase 1 Subcohort D2 only: Exclusion of isolated extramedullary disease (defined as any subject with ≤5% blasts in the bone marrow and confirmation of the presence of clonal blasts in any tissue other than the medullary compartments)

Statistical Methods

Sample Size

The sample size in Phase 1 Part A (dose escalation) of the study will be approximately 100, i.e., approximately 70 subjects with NHL and approximately 30 subjects with B cell ALL, depending on the number of dose levels and cohorts evaluated, and the occurrence of DLTs.

In Phase 1 Part B (cohort expansion), the sample size will be up to 30 subjects.

To test for efficacy, group sequential design with error-spending function will be employed. One interim analysis for futility and efficacy will be performed at an information level of 0.5 (proportion of total subjects), and boundaries based on error-spending function will be used for the interim analysis.

[redacted]

[redacted]

Endpoints

Primary Endpoints

- **Phase 1 Part A (dose escalation) for all cohorts**: The incidence of AEs, defined as DLTs for each of the cohorts (A, B, C, and D)
- **Phase 1 Part B (cohort expansion) and Phase 2**: The objective response rate (CR + PR) per the Lugano Response Criteria for Malignant Lymphoma, as determined by independent central review

Secondary Endpoints (Phase 1 Dose Escalation and Cohort Expansion and Phase 2)

Efficacy

- Duration of response/remission (central read/assessment)
- Duration of clinical benefit (central read/assessment)
- Treatment-failure–free survival
- Progression-free survival
- Overall survival
- For adult B cell ALL (Phase 1 Cohort D): ORR (CR + complete remission with incomplete blood count recovery [CRi])

Safety

- Frequency and severity of AEs and clinically significant laboratory abnormalities

Pharmacokinetic

- Levels of CTX110 in blood over time

Patient-reported Outcomes

- Change over time in PROs

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Term
AAV	adeno-associated virus
ADL	Activities of Daily Living
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
β2M/B2M	beta-2 microglobulin
BiPAP	bilevel positive airway pressure
BM	Bone marrow
CAR	chimeric antigen receptor
CARTOX	CAR T cell-therapy-associated TOXicity
Cas9	CRISPR-associated protein 9
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CIHHV-6	chromosomally integrated human herpesvirus 6
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPAP	continuous positive airway pressure
CR	complete response or complete remission
CRF	case report form
CRi	complete remission with incomplete blood count recovery
CRISPR	clustered regularly interspaced short palindromic repeats
CRP	C-reactive protein
crRNA	crispr RNA
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DES	DLT evaluable set
DL	dose level
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DOCB	duration of clinical benefit
DOR	duration of response
DSB	double-stranded break
DSMB	data safety monitoring board
EC	ethics committee

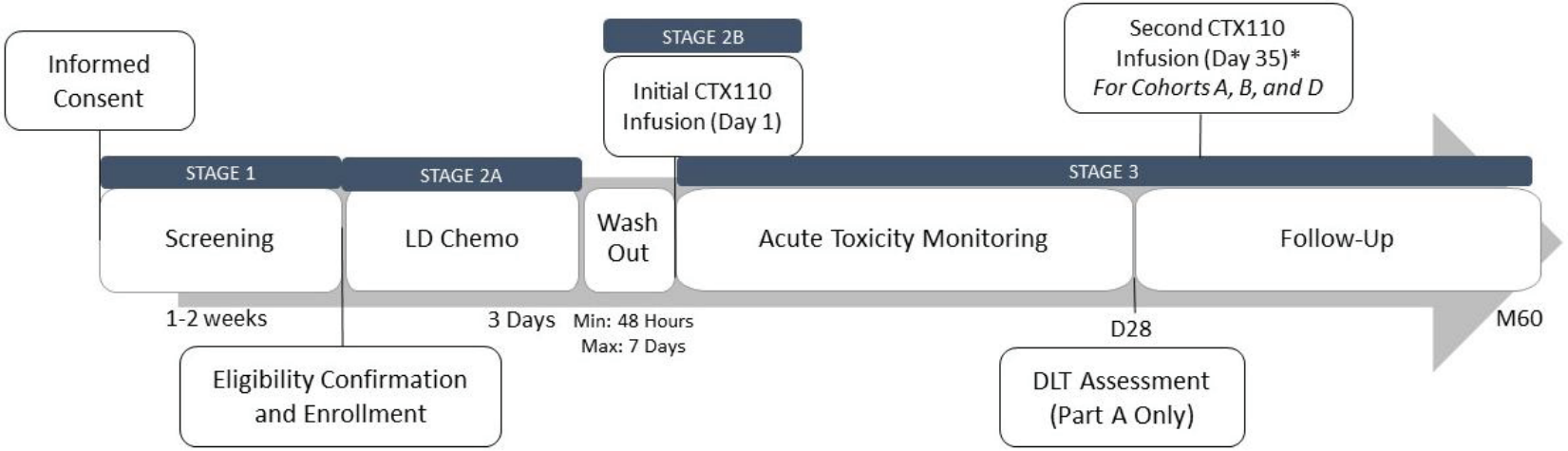
Abbreviation	Term
EC_{90}	90% effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEG	electroencephalogram
EFS	event-free survival
EQ-5D-5L	EuroQoL Group 5-Dimension
FACIT	Functional Assessment of Chronic Illness Therapy
FACT/-G/-Lym/Leu	Functional Assessment of Cancer Therapy/-general/-subscale for lymphoma/leukemia
FAS	full analysis set
FDG or F^{18} FDG	fluorodeoxyglucose or fluorodeoxyglucose F^{18}
FL	follicular lymphoma
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GTD	greatest traverse diameter
GvHD	graft vs host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HDR	homology-directed repair
HHV-6	human herpesvirus 6
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplant
HSV	herpes simplex virus
ICANS	immune effector cell–associated neurotoxicity syndrome
ICE	immune effector cell–associated encephalopathy
ICF	informed consent form
ICH	International Conference on Harmonisation
ICP	intracranial pressure
Ig	immunoglobulin
IL	interleukin
IPI	International Prognostic Index
IRB	institutional review board
IV	intravenous(ly)
KO	knockout
LBCL	large B cell lymphoma
LD	lymphodepleting
LP	lumbar puncture
MAGIC	Mount Sinai Acute GVHD International Consortium
MCL	mantle cell lymphoma

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MM	multiple myeloma
MRD	minimal residual disease
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NGS	next-generation sequencing
NHEJ	nonhomologous end-joining
NHL	Non-Hodgkin lymphoma
NK	natural killer
NOS	not otherwise specified
NR	not reached
ORR	objective response rate
OS	overall survival
PAM	protospacer-adjacent motif
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease/progression of disease
PET	positron emission tomography
PFS	progression-free survival
Ph+	Philadelphia chromosome-positive
PK	pharmacokinetic(s)
PMBCL	primary mediastinal large B cell lymphoma
PO	per os (orally)
PPD	product of the perpendicular diameters
PR	partial response
PRO	patient-reported outcome
R-CHOP	chemoimmunotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R/R	relapsed or refractory
SAE	serious adverse event
SAS	safety analysis set
SC	subcutaneous
scFv	single-chain variable fragment
SD	stable disease
SF-36	Short Form Survey Instrument
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
sgRNA	single-guide RNA
SPD	sum of product diameters
SRC	safety review committee

Abbreviation	Term
TAA	tumor-associated antigen
TBNK	T-, B-, natural killer (cells)
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TFFS	treatment-failure–free survival
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
TRAC	T cell receptor alpha constant
tracrRNA	trans-activating crRNA
ULN	upper limit of normal
VAS	visual analogue scale
VZV	varicella zoster virus

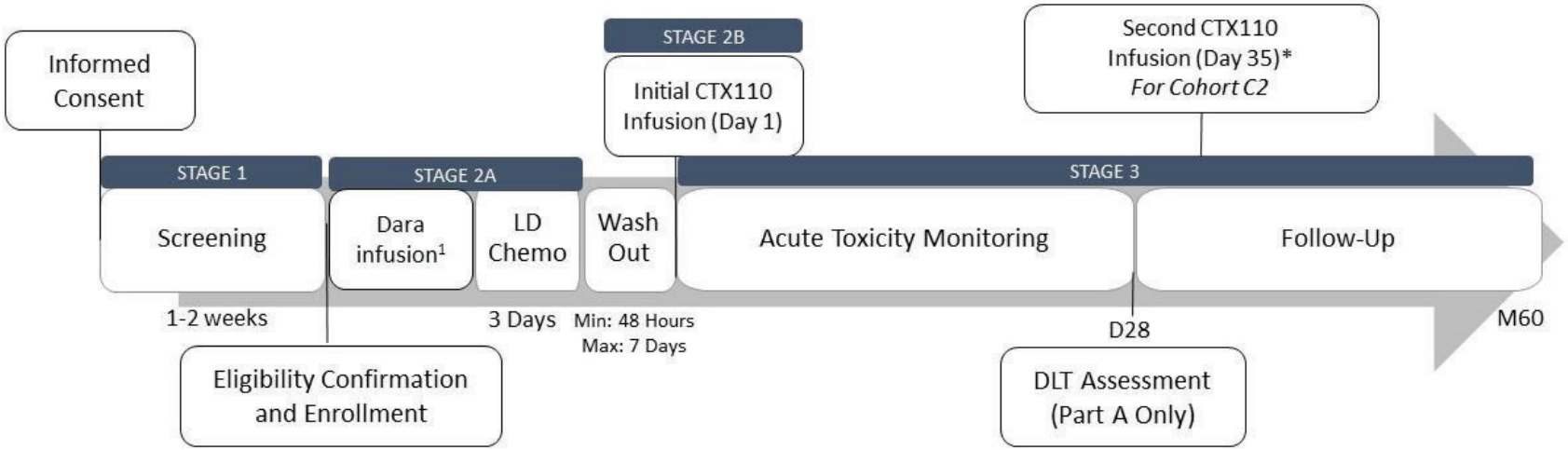
STUDY SCHEMA PHASE 1

Phase 1 Cohorts A, B, and D: Day 1 and Day 35 CTX110 Infusions Within the First Course of Treatment



ALL: acute lymphoblastic leukemia; BM: bone marrow; D: day; DLBCL: diffuse large B cell lymphoma; DLT: dose-limiting toxicity; FL: follicular lymphoma; IV: intravenously; LD: lymphodepleting; M: month; MRD: minimal residual disease; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; SD: stable disease.
Cohorts A and B will enroll subjects with NHL subtypes: DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, grade 3b FL, transformed FL, or primary mediastinal large B cell lymphoma. Cohort D (Subcohorts D1 and D2) will enroll subjects with B cell ALL.
For Cohorts A and D, LD chemotherapy comprises co-administration of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 IV daily for 3 days. For Cohort B, LD chemotherapy comprises co-administration of fludarabine 30 mg/m^2 and cyclophosphamide 750 mg/m^2 IV daily for 3 days.
* Subjects in Cohorts A, B, and D who achieve a clinical response on Day 28 (SD or better for NHL subjects and a decrease in BM blast count of ≥50% but blast count remains >5% or MRD positivity for adult B cell ALL subjects) will receive a second infusion of CTX110 on Day 35 (-7 days/+21 days) with LD chemotherapy (or without LD chemotherapy if the subject is experiencing significant cytopenia) if they meet the protocol-specified criteria (Section 5.3.1).
For Cohort B, LD chemotherapy prior to the second infusion will be co-administration of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 IV daily for 3 days.
Note: The first course of treatment will comprise the first (Day 1) and the second (Day 35) CTX110 infusions and associated LD regimen, as applicable.
Note: For all cohorts, subjects may receive a second course of treatment with a single CTX110 infusion with LD chemotherapy upon disease progression if a subject has had prior clinical response after the first infusion and meets the criteria for an additional infusion (Section 5.3.1.4).

Phase 1 Cohort C: Day 1 and Day 35 CTX110 Infusions Within the First Course of Treatment



ALL: acute lymphoblastic leukemia; BM: bone marrow; CR: complete response; D: day; Dara: daratumumab; DLBCL: diffuse large B cell lymphoma; DLT: dose-limiting toxicity; FL: follicular lymphoma; IV: intravenous; LD: lymphodepleting; M: month; MRD: minimal residual disease; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; SC: subcutaneous; SD: stable disease; SRC: safety review committee.

Cohort C (Subcohorts C1 and C2) will enroll subjects with NHL subtypes: DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, grade 3b FL, transformed FL, or primary mediastinal large B cell lymphoma.

Subjects will receive an IV infusion (16 mg/kg) or SC injection (1800 mg) of daratumumab followed by LD chemotherapy (co-administration of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 IV daily for 3 days). Daratumumab will be administered at least 1 day prior to starting LD chemotherapy and within 10 days prior to CTX110 infusion. CTX110 will be administered 48 hours to 7 days after LD chemotherapy. For subjects in Subcohorts C1 who achieve SD or better (on Day 28, 2 additional doses of daratumumab (16 mg/kg IV or 1800 mg SC) will be administered at the Day 28 (± 4 days) and Month 2 (± 4 days) visits. Subcohort C1 will not receive any additional CTX110 infusion on Day 35 (-7 days/+21 days).

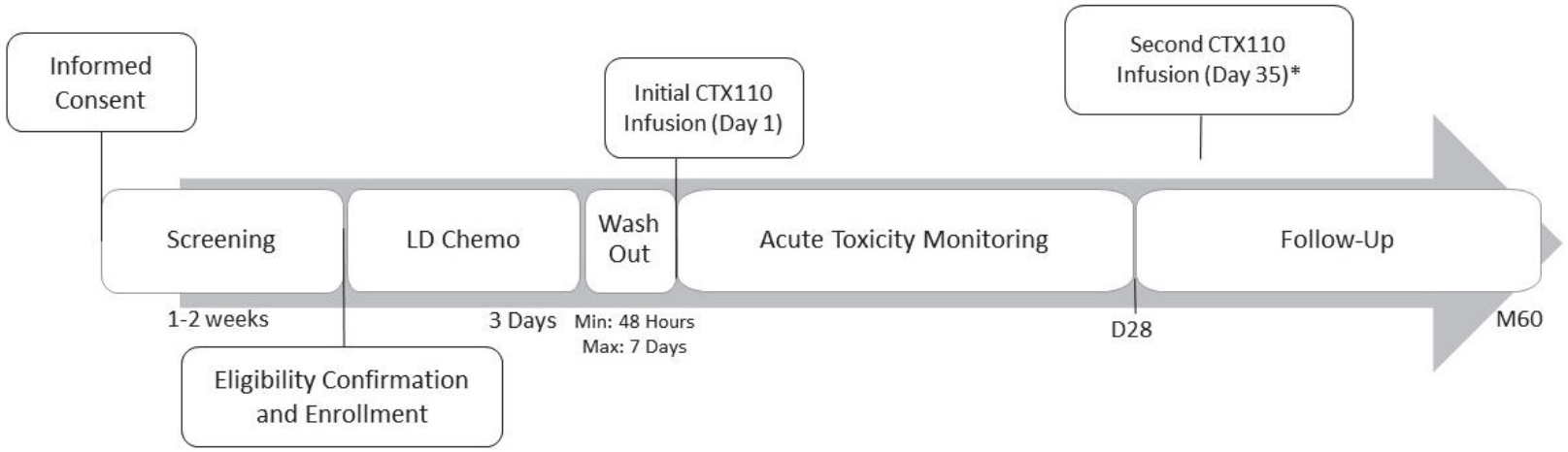
* Subjects in Subcohort C2 who achieve a clinical response on Day 28 (SD or better for NHL subjects and a decrease in BM blast count of ≥50% or MRD positivity for adult B cell ALL subjects) will receive a second infusion of CTX110 on Day 35 (-7 days/+21 days) with daratumumab and LD chemotherapy (or without LD chemotherapy if the subject is experiencing significant cytopenia) if they meet the protocol-specified criteria (Section 5.3.1). For subjects who are eligible for an additional infusion of CTX110 on Day 35, the Day 28 daratumumab administration will be repeated as part of LD regimen unless received within 14 days prior to the additional CTX110 infusion.

Note: The first course of treatment will comprise the first (Day 1) and the second (Day 35) CTX110 infusions and associated LD regimen, as applicable.

Note: For all cohorts, subjects may receive a second course of treatment with a single CTX110 infusion with LD chemotherapy after disease progression if a subject has had prior objective response within 18 months of the initial CTX110 infusion and ≥4 weeks from the prior CTX110 infusion and meets the criteria for an additional infusion (Section 5.3.1.4). The second course of treatment will be administered with standard lymphodepletion (i.e., without daratumumab).

STUDY SCHEMA PHASE 2

Phase 2 for Subjects with NHL: Day 1 and Day 35 CTX110 Infusions Within the First Course of Treatment



D: day; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; LD: lymphodepleting; M: month; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; SD: stable disease.

Phase 2 will enroll subjects with NHL subtypes: DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, grade 3b FL, transformed FL, or primary mediastinal large B cell lymphoma.

LD chemotherapy comprises co-administration of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 IV daily for 3 days. The dose level for each CTX110 infusion will be 6×10^8 CAR$^+$ T cells.

* Subjects who achieve a clinical response on Day 28 (SD or better) will receive a second infusion of CTX110 on Day 35 (-7 days/+21 days) with LD chemotherapy (or without LD chemotherapy if the subject is experiencing significant cytopenia) if they meet the protocol-specified criteria (Section 5.3.1).

Note: The first course of treatment will comprise the first (Day 1) and the second (Day 35) CTX110 infusions and associated LD regimen, as applicable.

Note: Subjects may receive a second course of treatment with a single CTX110 infusion with LD chemotherapy upon disease progression if a subject has had prior clinical response after the first infusion and meets the criteria for an additional infusion (Section 5.3.1.4).

1. INTRODUCTION

This study will evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamic effects of CTX110, an allogeneic chimeric antigen receptor (CAR) T cell therapy, in subjects with relapsed or refractory B cell malignancies.

1.1. $CD19^+$ B Cell Malignancies

CD19 is a type I transmembrane protein and belongs to the immunoglobulin (Ig) superfamily. CD19 is typically found in a complex with CD81 and CD21 and plays important roles in B cell activation and signaling. CD19 is expressed in B cells and follicular dendritic cells. Genetic perturbations of CD19 in mice or humans lead to defects in B cell function and impaired immune responses (Wang et al., 2012). CD19 is expressed by most B cell leukemia and lymphoma cells and has been the target of several therapeutic modalities, including antibodies such as blinatumomab and CD19-directed CAR T cells.

1.2. Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies originating from B lymphocytes, T lymphocytes, or natural killer (NK) cells. The World Health Organization defines more than 60 different subcategories of NHL based on cell type in which the cancer originates, histology, mutational profiling, and protein markers on the cellular surface, and NHL is the tenth most common malignancy worldwide (Chihara et al., 2015; Trask et al., 2012). NHL accounts for 4.3% of all new cancer cases reported and is the eighth leading cause of cancer deaths in the United States. In 2018, it is estimated that 74,680 NHL cases will be reported, with approximately 19,910 NHL-associated deaths (National Cancer Institute, 2018). In Europe, the crude incidence of NHL is approximately 3.8/100,000/year (Tilly et al., 2015). The major subtypes of NHL include diffuse large B cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), and follicular lymphoma (FL; (Teras et al., 2016; Trask et al., 2012). CD19 expression is ubiquitous on B cell malignancies and maintained among indolent and aggressive subtypes of NHL (Scheuermann and Racila, 1995), which has contributed to the increase of development of CD19-directed therapies in these indications

1.2.1. Diffuse Large B Cell Lymphoma

DLBCL is the most common type of NHL, accounting for 30-40% of diagnosed cases (Sehn and Gascoyne, 2015). Approximately 30-50% achieve cure with first-line chemoimmunotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; (Coiffier et al., 2010; Maurer et al., 2016). However, approximately 20% are refractory to R-CHOP and 30% relapse following complete response (CR) (Maurer et al., 2016).

In patients who relapse after R-CHOP, the best long-term clinical outcomes are achieved through [redacted] hematopoietic stem cell transplant (HSCT). For patients who are healthy enough to undergo this procedure and have chemosensitive disease, commonly used induction chemotherapy consists of either R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin). In a large randomized trial of R-ICE vs R-DHAP in transplant-eligible subjects with DLBCL (the CORAL study), 63% of

subjects achieved an objective response to either regimen, with a 26% CR rate (Gisselbrecht et al., 2010). For patients who are not eligible for [redacted] treatment options are limited and focused on palliation (Friedberg, 2011; Maurer et al., 2016; Raut and Chakrabarti, 2014).

For patients with progressive disease (PD) after 2 or more lines of therapy, prognosis continues to be poor, with an estimated median survival of 3 months for patients who relapse following [redacted] (Friedberg, 2011). In those cases, allogeneic HSCT is an option but only for the limited number of patients who qualify based on performance status and presence of chemosensitive disease (Raut and Chakrabarti, 2014; Sarkozy et al., 2015).

The poor outcomes in the relapsed/refractory population were further highlighted in the recent SCHOLAR study, which retrospectively analyzed survival and response rates in more than 600 subjects with relapsed/refractory DLBCL, transformed FL, and primary mediastinal large B cell lymphoma (PMBCL). The outcomes demonstrated an overall response rate of 26% (CR rate of 7%) and median overall survival of 6.3 months, further emphasizing the need for curative treatment options in this setting (Crump et al., 2017). Although the advent of cellular immunotherapy and autologous CAR T cells has presented potential options to relapsed/refractory patients with DLBCL, the duration of follow-up has been short. Furthermore, there have been challenges surrounding manufacturing of autologous cellular products, the duration of manufacturing, and the need for bridging chemotherapy, all of which may be addressed by an allogeneic off-the-shelf CAR T cell product.

1.2.2. Follicular Lymphoma Grade 3b and Transformed Follicular Lymphoma

FL is a heterogeneous disease, usually indolent, and accounts for about 20% of reported NHL. The course is characterized by initial response to therapies followed by relapse and, at times, transformation to a more aggressive form of lymphoma. It is generally considered incurable at more advanced stages, although the 10-year survival rate is 71% for subjects with early-stage disease and 0 to 1 risk factors based on Follicular Lymphoma International Prognostic Index score (Solal-Céligny et al., 2004). FL is divided into grades 1-3 based on histologic assessment and proportion of centrocytes to centroblasts, and grade 3 is subdivided into 3a and 3b. FL grade 3b is now considered a biologically distinct entity, with frequent absence of t(14;18) and CD10 expression, and increased p53 and MUM1/IRF4 expression (Horn et al., 2011). A large retrospective analysis of more than 500 FL cases further confirmed that the clinical course of FL grade 3a is similar to FL grade 1-2, whereas FL grade 3b has a clinical course more similar to that of DLBCL (Kahl and Yang, 2016; Wahlin et al., 2012). Because of this, FL grade 3b is typically managed similarly to DLBCL (Kahl and Yang, 2016).

FL patients are at risk of transformation to an aggressive form of lymphoma at a rate of 9-17% at 5 years and 15-30% at 10 years, as observed in retrospective studies (Bains et al., 2013; Giné et al., 2006). Initial treatment approaches are driven by prior therapies; however, even in the rituximab era, the outcomes are poor (Fischer et al., 2018). A study comparing outcomes of subjects with DLBCL and FL found that FL subjects relapsing with transformed disease had worse outcomes compared with subjects diagnosed with de novo DLBCL (median survival 2 years vs 6 years, $P < .0003$; (Jack et al., 2013). Treatment options for relapsed/refractory transformed FL remain similar to DLBCL, with comparably poor outcomes, further underlining the unmet medical need in this patient population.

1.2.3. High Grade Lymphoma

High grade B cell lymphoma refers to cases of lymphoma that morphologically resemble DLBCL but also contain *MYC* and *BCL2* and/or *BCL6* rearrangements (also referred to as "double hit" / "triple-hit" lymphoma). This diagnosis was established in the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms (Swerdlow et al., 2016).

Incidence of high grade B cell lymphoma is variable across studies, affecting approximately 8% (Green et al., 2012; Scott et al., 2018) of patients with DLBCL morphology. Some studies observed a hit rate of up to 21% (Johnson et al., 2012).

MYC, *BCL2*, and *BCL6* rearrangements are diagnosed by fluorescence in situ hybridization or cytogenetics. The MYC transcription factor regulates the expression of genes involved in the cell cycle, DNA damage repair, metabolism, protein synthesis, and response to stress (Dang et al., 2006). *MYC* translocations are predominantly observed in the germinal B cell–like cell-of-origin subtype (Scott et al., 2018). B cell lymphoma-2 (BCL2) is an anti-apoptotic protein (Opferman and Kothari, 2018). In the event of a translocation of chromosomes 14 and 18, t(14; 18), the *BCL2* transcription is constitutively dysregulated resulting in a survival advantage for affected B cells. Most *BCL2* translocations occur in the germinal B cell–like subtype. B cell lymphoma-6 (BCL6) is expressed in normal mature germinal center B cells and acts as a transcription repressor. However, when BCL6 is overexpressed, it acts as a proto-oncogene by suppressing p53 and preventing apoptosis in response to DNA damage in germinal center B cells.

High grade B cell lymphoma is associated with an aggressive clinical course with overall inferior prognosis compared to DLBCL when treated with standard of care combination of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) chemotherapy (Green et al., 2012; Horn et al., 2013; Hu et al., 2013; Johnson et al., 2012). Until the recently available data from an ongoing trial (POLARIX; NCT03274492), intensified induction regimens were not shown to improve outcomes in the past 20 years (D¨uhrsen, 2018). The median overall survival for high grade lymphoma ranges from 4.5 to 34 months (Akyurek et al., 2012; Bertrand et al., 2007; Johnson et al., 2009; Kanungo et al., 2006; Le Gouill et al., 2007; Lin and Medeiros, 2007; Niitsu et al., 2009; Oki et al., 2014; Petrich et al., 2014; Ye et al., 2015). This poor prognosis results from the increased risk of central nervous system involvement, the higher risk of chemoimmunotherapy refractoriness, and the increased rate of relapse (Kesavan et al., 2019). Additionally, autologous stem cell transplantation in the relapse setting is associated with poor outcomes (Cuccuini et al., 2012).

1.2.4. Primary Mediastinal Large B Cell Lymphoma

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare type of NHL that accounts for 2% to 3% of NHL cases and tends to impact adolescents and young adults, predominantly white women age 30 to 39 (Yu et al., 2021). First-line treatments include dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab with or without radiotherapy and R-CHOP combined with radiotherapy. For relapsed or refractory patients (10%-30% of total cases), the PD-1 inhibitor pembrolizumab was shown in a Phase 2 study to have an ORR of 45%, with 13% of 53 subjects achieving CR and 32% partial response (PR). PD-1 monoclonal antibodies have been shown to further improve efficacy in patients with relapsed/refractory PMBCL when combined with chemotherapy; camrelizumab combined with

gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD) produced an ORR of 74%, with 56% of 27 subjects achieving CR, and nivolumab combined with brentuximab vedotin produced an ORR of 73%; however, more AEs were observed than from pembrolizumab alone. Of note, PD-1/PD-L1 inhibitors combined with platinum-based chemotherapies have also shown efficacy.

Autologous CAR T cell therapies have been evaluated in patients with R/R PMBCL and, although patient numbers are small, therapeutic potential has been observed in the ZUMA-1 study (ORR = 82% for 101 total patients, including 8 patients with relapsed/refractory PMBCL) and in the transcend NHL-001 study (CR = 53% for the 15 patients with R/R PMBCL).

1.3. Adult Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by highly proliferative immature lymphoid cells in the bone marrow and peripheral blood. In adults, ALL accounts for approximately 20% of all leukemias, the second most common, with an incidence of more than 6,500 cases per year in the United States alone (Terwilliger and Abdul-Hay, 2017). ALL carries a poor prognosis in adults, with a 5-year overall survival of 24% in patients ages 40 to 59 years, and 18% in patients ages 60 to 69 years (Terwilliger and Abdul-Hay, 2017; Wang et al., 2015).

The hallmark of ALL is chromosomal abnormalities and genetic alterations involved in differentiation and proliferation of lymphoid precursor cells. The main goal of treatment is to allow the patient to achieve complete remission (CR) and to consolidate this remission with either a maintenance regimen or an allogeneic stem cell transplant.

The backbone of front-line therapy remains multi-agent chemotherapy (e.g., vincristine, corticosteroids, and an anthracycline) followed by an allogeneic stem cell transplantation for eligible candidates. Elderly patients are often unable to tolerate the intense chemotherapy regimen and have a particularly poor prognosis. Despite a high rate of response to induction chemotherapy, only 30-40% of adult patients with ALL will achieve long-term remission (Terwilliger and Abdul-Hay, 2017).

Adult patients with relapsed or refractory ALL have poor outcomes, with survival of less than 6 months. Treatment options in the salvage setting are limited to conventional cytotoxic chemotherapy, which have minimal activity, necessitating the development of novel therapies to improve outcomes (Paul et al., 2019). Advances in the development of novel targeted therapies include: antibody-based therapies such as blinatumomab (bispecific T cell–engaging antibody engineered to form a synapse between CD3 T cells and CD19 B cells) and inotuzumab ozogamicin (CD22-directed antibody linked to calicheamicin that causes double-stranded DNA breaks that lead to apoptosis once released in the target cell); and CAR T cell therapy in relapsed or refractory ALL, which has made possible an approach to treatment that is more effective and patient-centered than the historical standard chemotherapies. These new advances have provided patients with additional options in relapsed setting, although outcomes remain poor. For example, subjects with relapsed or refractory ALL who received inotuzomab achieved a CR/ complete remission with incomplete blood count recovery (CRi) rate of 88%, with a median duration of response (DOR) of 5.4 months (Kantarjian et al., 2016). Blinatumomab was approved in subjects with relapsed/refractory ALL based on a CR rate of 34% and median DOR

of 7.3 months. However, the need for continuous administration of the product and associated adverse events have made it challenging (Kantarjian et al., 2017).

CAR T cell therapy is revolutionizing the treatment of both pediatric and adult relapsed or refractory B cell ALL (Table 1). The promising efficacy of the CD19-directed CAR T cell tisagenlecleucel (Kymriah®, Novartis) in a Phase 1/2a clinical trial led to a Phase 2 clinical trial in pediatric and young adult patients with relapsed or refractory ALL, and its US approval in 2017. Another CD19-directed CAR T cell product, brexucabtagene autoleucel (Tecartus®, Kite Pharma), is approved in the US for treatment of relapsed or refractory B cell precursor ALL supported by the Phase 1/2 ZUMA-3 clinical trial (Shah et al., 2021; Wierda et al., 2018).

Table 1: CAR T Cell Clinical Trial Results in ALL

Clinical Trial	**Pedi CART19**	**ELIANA**	**MSKCC***	**ZUMA-3**
Costimulatory Domain	**4-1BB (Maude 2014) [1]**	**4-1BB (Maude 2018, Grupp 2018) [2]**	**CD28 (Park 2018) [3]**	**CD28 (Shah 2021) [4]**
Number of subjects [5]	30	79	53	55
Treatment setting	R/R pediatric and adult ALL	R/R pediatric and young adult ALL	R/R adult ALL	R/R adult ALL
CR rate	90%	82%	83%	71% [6,7]
Estimated EFS				
6 months 12 months 18 months	67% NR NR	73% 50% 66%	Median 6.1 months	Median 11.6 months[8]
Estimated OS				
6 months 12 months 18 months	78% NR NR	90% 76% 70%	Median 12.9 months	Median 18.2 months [6]

ALL: acute lymphocytic leukemia; CAR: chimeric antigen receptor; CR: complete remission; EFS: event-free survival; MSKCC: Memorial Sloan Kettering Cancer Center; N/A: not available; NR: not reached; OS: overall survival; R/R: relapsed or refractory
[1] Maude et al. (2014b); NCT01626495
[2] Maude et al. (2018) and (Grupp et al., 2018); NCT02435849
[3] Park et al. (2018); NCT01044069
[4] Shah et al. (2021); NCT02614066
[5] Subjects who received infusion
[6] Subjects treated with 1×10^6 CAR^+ T cells/kg
[7] CR or CR with incomplete hematological recovery
[8] Reflects relapse-free survival
*The clinical trial was conducted by MSKCC.

Despite toxicities associated with CAR T cell therapies, clinicians remain interested because of the responses seen with this approach. To overcome the logistic challenges associated with autologous CAR T cell therapies, allogeneic 'off-the-shelf' CAR T cells are currently being investigated in clinical trials (Paul et al., 2019). The CALM and PALL studies evaluated the safety and activity of the allogeneic CD19 CAR T cell (UCART19) in adult and pediatric

subjects with relapsed or refractory ALL. A total of 21 subjects received at least 1 UCART19 infusion of whom 14 (67%) achieved CR or CRi, and 10 of the 14 (71%) subjects achieved [redacted] [redacted] CRS was observed in 19 subjects (91%; grade 1-2, n = 16; grade >3, n = 3) (Benjamin et al., 2020). A Phase 1 clinical trial of another allogeneic CAR T cell therapy, PBCAR019, which uses homing endonuclease technology to insert a CD19 CAR, reported positive initial data for 9 treated subjects with NHL or B cell ALL (Jacobson et al., 2019); see also Section 1.5.2). This further underlines a continued interest in allogeneic CAR T cell therapies for B cell ALL indication and the unmet medical need for relapsed/refractory patients.

1.4. CAR T Cell Therapy

CAR T cell therapies are a form of adoptive T cell therapeutics used to treat human malignancies (Rosenberg and Restifo, 2015). These treatments consist of T cells, usually from the cancer patient (autologous), that are genetically manipulated ex vivo to target tumor-associated antigens (TAAs) before infusion back into the patient.

CARs are synthetic modular proteins that consist of an extracellular target-binding domain with the ability to recognize and bind to a tumor cell–specific ligand, a hinge region, a transmembrane domain that anchors the CAR to the cell membrane, and an intracellular signaling domain that results in T cell activation upon antigen binding (Gill and June, 2015). The target-binding domain consists of a single-chain variable fragment (scFv) derived from an antibody that confers major histocompatibility complex (MHC)–independent TAA specificity and is expressed on the surface of the CAR T cell. The scFv is linked to a transmembrane domain that is linked to T cell signaling domains. These T cell signaling domains can include a signaling region of the CD3ζ molecule or the FcRγ chain as well as a costimulatory domain to provide additional signaling output downstream of ligand engagement. The most common costimulatory domains in current clinical use are derived from the CD28 or CD137 (4-1BB) proteins (Gill and June, 2015).

1.5. Clinical Experience With CAR T Cell Therapy

The past decade has seen intensive nonclinical and clinical research in the field of CAR T cell therapies for both hematological malignancies and solid tumors. A variety of approaches are currently under investigation and include CAR T cells engineered with different (1) extracellular target domains, (2) intracellular signaling domains, (3) sources of T cells (e.g., autologous vs allogeneic), and (4) genetic approaches to encode and deliver the CAR and induce other cell-specific modifications, such as knocking out cell surface proteins.

1.5.1. Autologous CAR T Cells

The most advanced clinical data on CAR T cells come from studies involving autologous CD19-directed CAR T cells (Maude et al., 2015; Neelapu et al., 2017; Schuster et al., 2019). Autologous CAR T cell products are manufactured using a patient's own T cells, which are collected via apheresis. For commercial CD19-directed CAR T cell therapies, isolated T cells are either selected or expanded ex vivo, then transduced with a retroviral or lentiviral vector for the stable integration and expression of the anti-CD19 CAR construct. The CAR T cell product is infused into the patient after lymphodepleting (LD) chemotherapy, approximately 2 to 8 weeks after initial T cell collection. During this time, some patients may receive bridging chemotherapy to keep their disease in control while awaiting the final product.

Following infusion, CAR T cells undergo significant expansion of up to 100,000-fold in vivo, with later redistribution and persistence, in some cases reported for years following infusion. CAR T cells have also been documented to traffic into the cerebrospinal fluid (CSF), bone marrow, and tumor tissue (June et al., 2018). During the expansion of CAR T cells, many patients experience some degree of cytokine release syndrome. Patients may also develop neurotoxicity, the pathophysiology of which is not fully understood, with suspected contributing factors including [redacted] CAR T cells trafficking in CSF, and/or increased permeability of the blood brain barrier. Some patients may also experience prolonged neutropenia and thrombocytopenia, likely due to a combination of underlying disease, CRS with resulting immunosuppression, and LD chemotherapy. Other toxicities experienced by patients receiving CAR T cell therapies include infections, hemophagocytic lymphohistiocytosis (HLH), and hypogammaglobulinemia. The latter is a direct result of persistent CD19-directed CAR T cells, which do not differentiate between CD19 expressed on tumor cells and on normal B cells. The majority of these toxicities have been successfully managed, and many patients have achieved durable complete responses with autologous CAR T cell therapy. Several completed clinical trials have led to the US Food and Drug Administration and European Medicines Agency approvals of tisagenlecleucel for pediatric and young adult relapsed/refractory ALL and adult relapsed/refractory DLBCL; axicabtagene ciloleucel for adult relapsed/refractory DLBCL, PMBCL, and transformed FL; and lisocabtagene maraleucel (BREYANZI®, Juno/Bristol-Myers Squibb) for adult patients with relapsed or refractory large B cell lymphoma after 2 or more lines of systemic therapy, including DLBCL NOS (including DLBCL arising from indolent lymphoma), high-grade B cell lymphoma, PMBCL, and FL grade 3B (Maude et al., 2015; Neelapu et al., 2017; Schuster et al., 2017).

In the pivotal trial of axicabtagene ciloleucel involving 101 subjects with relapsed/refractory DLBCL, PMBCL, and transformed FL treated with autologous CAR T cells, the ORR was 72%, with a DOR of 9.2 months. The CR rate was 51% and the DOR has not yet been established. Grade ≥3 CRS and neurologic events occurred in 13% and 28% of subjects, respectively (Yescarta USPI, 2017).

The efficacy and safety of tisagenlecleucel was evaluated in an open-label, multicenter, single-arm trial in adult subjects with relapsed or refractory DLBCL who had received at least 2 lines of chemotherapy. Of the 160 subjects enrolled, 106 subjects received tisagenlecleucel, including 92 subjects who were followed for at least 3 months or discontinued earlier. Of the 160 subjects enrolled, 49 did not receive tisagenlecleucel due to manufacturing failures, death, adverse events (AEs), or physician's choice. Among the efficacy evaluable population of 68 subjects, efficacy was established based on CR rate and DOR. The ORR was 50% and CR rate was 32%. With a median follow-up of 9.4 months, median DOR in responders and subjects who achieved CR has not been reached. Grade ≥3 CRS and neurotoxicity occurred in 23% and 18% of subjects, respectively (Kymriah USPI, 2017).

The approval of lisocabtagene maraleucel is based on the efficacy and safety results from the Transcend NHL001 pivotal trial results in which 268 subjects with relapsed/refractory large B cell lymphoma received the treatment, including subjects with broad range histologies and high-risk disease. In the study, 192 subjects were treated at the dose of 50 to 110 × 10^6 CAR^+ viable T cells and evaluated for efficacy. Of these subjects, 73% achieved a response (95% confidence interval [CI]: 67%-80%), including 54% who had minimal or no detectable lymphoma remaining following treatment (CR; 95% CI: 47%-61%) and 19% who achieved a

partial response (PR; 95% CI: 14%-26%). Median DOR was 16.7 months in all responders (95% CI: 5.3 – not reached [NR]). For subjects who achieved a CR, median DOR was NR (95% CI: 16.7 – NR), and for subjects with a best response of PR, median DOR was 1.4 months (95% CI: 1.1 – 2.2). Of 104 subjects treated with lisocabtagene maraleucel who achieved a best overall response of CR, 65% had remission lasting at least 6 months and 62% had remission lasting at least 9 months. In the study, 268 subjects treated with lisocabtagene maraleucel were evaluated for safety. Any grade CRS occurred in 46% (122/268) of subjects using the Lee grading system (Lee et al., 2014). Grade ≥3 CRS and grade ≥3 neurological toxicities occurred in 4% (11/268) and 12% (31/268) of subjects, respectively (Breyanzi USPI, 2021).

These approvals have paved the way to further exploration of CAR T cell therapies and have identified further areas of improvement in which an off-the-shelf allogeneic product could have appropriate use.

1.5.2. Allogeneic CAR T Cells

Allogeneic CAR T cells (manufactured from T cells collected from a healthy donor) have also been investigated for hematological malignancies such as pediatric ALL. Whereas allogeneic HSCT requires a human leukocyte antigen (HLA)–matched donor, gene editing allows the removal of cell surface proteins most likely to cause graft vs host or host vs graft reactions.

Early phase clinical studies are ongoing evaluating UCART19, an allogeneic CAR T cell therapy that combines lentiviral-driven expression of a CD19 CAR with the use of TALEN (transcription activator-like effector nucleases) gene editing to knock out the T cell receptor (TCR) and CD52 (ClinicalTrials.gov Identifiers: NCT02808442, NCT02746952; Section 1.3). Study data demonstrate the safety of the approach, with only 2 reported cases of mild (grade 1) skin graft vs host disease (GvHD) in the 21 subjects treated, although the incidence of CRS and neurotoxicity remain similar to autologous CD19-directed CAR T cell therapy. No other GvHD has been reported in those studies, and 14 of 21 (67%) evaluable subjects demonstrated a CR or CRi (Benjamin et al., 2020). This approach demonstrates the safety of the allogeneic CAR T cells, with only 2 reported cases of mild GvHD in the 21 subjects treated. The risk of CRS and neurotoxicity remain and will continue to be managed as with autologous CAR T cell treatment. In the Phase 1 clinical trial evaluating another allogeneic CAR T therapy PBCAR019 in B cell malignancies (Jacobson et al., 2019); Section 1.3), early findings include no serious adverse events (SAEs) or dose-limiting toxicities (DLTs), and no cases of GvHD, with 7 of 9 subjects (78%) with objective evidence of tumor shrinkage at any time point. In the B cell ALL cohort, 3 subjects (mean age: 56 years; range: 48-72 years) treated at dose level (DL) 2 achieved Day 28+ ORR of 33% (1/3 patients at DL 2), comprising 1 CR. These subjects had received a median of 4 prior lines of therapy, and all 3 subjects were refractory to their last treatment, with 2 subjects having poor prognostic indicators at trial entry.

An overview of several external allogeneic CAR T cell programs in clinical development are presented in Table 2. Overall, initial data demonstrate the safety of the allogeneic CAR T cell approach. Compared to autologous CD19-directed CAR T cell therapy, the incidence of CRS and neurotoxicity remains similar and the events are less severe. In addition, studies of allogeneic CAR T cells demonstrate efficacy similar to that seen with autologous CAR T cells.

Table 2: Overview of Key Allogeneic CAR T Programs by Other Sponsors

Target Antigen	Indication	Engineering/ Modality	Dose Levels	Efficacy	Safety	Program and ClinicalTrials.gov Identifier #	Sponsor Reference
CD19	R/R LBCL or FL	TALEN TCR and CD52 KO for selective LD with ALLO-647	ALLO-501 DL1: 40 × 10^6 DL2: 120 × 10^6 DL3: 360 × 10^6 DL2 Consol.: 120 × 10^6 Day 0 and D28 for ≥SD ALLO-501a DL1: 40 × 10^6 DL2: 120 × 10^6 DL2 Consol.: 120 × 10^6 Day 0 and D28 for ≥SD	ALLO-501 ORR 75% (24/32), CR 50% (16/32) ALLO-501a ORR 56% (5/9), CR 56% (5/9)	ALLO-501 27% CRS any grade, no grade ≥3 CRS, 2% ICANS (any grade and grade ≥3), no GvHD ALLO-501a 15% CRS any grade, 8% CRS grade ≥3, no ICANS, no GvHD	ALLO-501 (ALPHA Study) NCT03939026 ALLO-501a (ALPHA2 Study) NCT04416984	Allogene CD19 Forum[1] (Neelapu et al., 2020)
BCMA	R/R MM	TALEN TCR and CD52 KO for selective LD with ALLO-647	DL1: 40 × 10^6 DL2: 160 × 10^6 DL3: 320 × 10^6 DL4: 480 × 10^6	ORR 60% (6/10) in DL3	45% (14/31) CRS grade 1 or 2, no ICANS, no GvHD	ALLO-715 (UNIVERSAL Study) NCT04093596	Allogene (ASH 2020 Abstract) (Mailankody et al., 2020)[2]
CD19	R/R B-ALL	TALEN TCR and CD52 KO for selective LD with alemtuzumab	(CALM) DL1: 6 × 10^6/kg DL2: 6-8 × 10^7/kg DL3: 1.8-2.4 × 10^8/kg (PALL) 1.1-2.3 × 10^6/kg	67% subjects (14/21) achieved CR or CRi	CRS any grade: 91% (19/21); grade 3 or 4 CRS: 14% (3/21); grade 1 or 2 neurotox: 38% (8/21); acute skin GvHD: 10% (2/21); grade 4 prolonged cytopenia: 32% (6/21)	UCART19 (CALM Study) NCT02746952 (PALL Study) NCT02808442	Cellectis (Benjamin et al., 2020)

Target Antigen	Indication	Engineering/ Modality	Dose Levels	Efficacy	Safety	Program and ClinicalTrials.gov Identifier #	Sponsor Reference
CD22	R/R B-ALL	TALEN TCR and CD52 KO for selective LD with ALLO-647	DL1: 1 × 10^5/kg DL2: 1 × 10^6/kg	2 of 3 subjects at DL1 achieved CRi and CR	3/5 subjects with CRS, no ICANS, no GvHD	UCART22 (BALLI-01 Study) NCT04150497	Cellectis (ASH 2020 Abstract) (Jain et al., 2020)
CD19	NHL B-ALL	Meganuclease TCR KO	DL1: 3 × 10^5/kg DL2: 1 × 10^6/kg DL3: 3 × 10^6/kg	NHL: ORR:11 subjects (100%) CR: 8 subjects (73%)	NHL: 56% (9/16) subjects with grade 1 or 2 CRS, 31% (5/16) subjects with grade 1 or 2 ICANS, no GvHD B-ALL: 45% (5/11) subjects with grade 1 or 2 CRS, 18% (2/11) subjects with grade 1 or 2 ICANS, no GvHD	PBCAR0191 (Phase 1/2 Study) NCT03666000	(Precision Biosciences, 2022)[3]
CD19	R/R B-NHL	PD-1 KO	DL1: 40 x 10^6 DL2: 80 x `10^6	CR: 40% at 6 months 100% best response Longest measured CR: 9 months	4 (67%) subjects with 17-related grade ≥3 TEAEs (neutropenia; 1 (17%); thrombocytopenia 3 (50%); WBC decreased 3 (50%); lymphocyte decreased 1 (17%); LDH increased 1 (17%)) Any grade: CRS 2 (33%) ICANS 1 (17%) (grade 3) Infection 2 (33%) (grade 3: 1 (17%)	CB-010 (ANTLER) NCT04637763	Caribou Biosciences (Nastoupil et al., 2022) (EHA 2022 Poster)

ASCO: American Society of Clinical Oncology; ASH: American Society of Hematology; B-ALL: B cell acute lymphoblastic leukemia; BCMA: B cell maturation antigen; Consol.: consolidation; CR: complete response; CRi: CR with incomplete hematologic recovery; CRS: cytokine release syndrome; DL: dose level; DLT: dose-limiting toxicity; DoR: duration of response; FL: follicular lymphoma; GvHD: graft vs host disease; ICANS: immune

effector cell–associated neurotoxicity syndrome; KO: knockout; LBCL: large B cell lymphoma; LD: lymphodepletion; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; ORR: objective response rate; PDL-1: programmed death ligand 1; PR: partial response; R/R: relapsed/refractory; SD: stable disease; TALEN: transcription activator-like effector nucleases; TCR: T cell receptor; WBC: white blood cell.

[1] Allogene Therapeutics CD19 Forum 19 May 2021 presentation available at https://ir.allogene.com/static-files/7a26a1c0-55f9-4474-a362-9a49b598c43c.

[2] Oral presentation available at: https://www.allogene.com/resources/download/Anti_BCMA_ALLO_715_And_Anti_CD52_Mab_ALLO_647.pdf

[3] Data disclosure available at: https://investor.precisionbiosciences.com/static-files/717d82d7-d304-4428-ba22-1a19c965d8d5

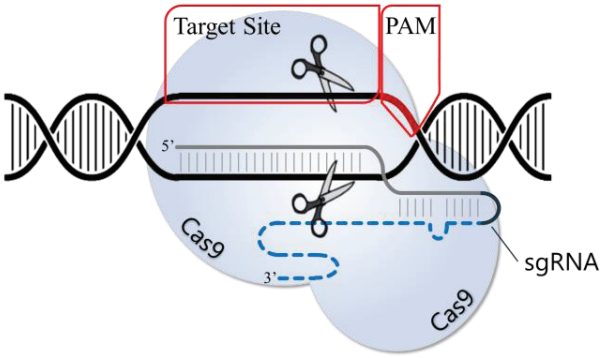
In addition, CRISPR Therapeutics currently has allogeneic CAR T cell programs in clinical development, including CTX110. Preliminary clinical data from CTX110 targeting CD19 being evaluated in subjects with relapsed or refractory B cell malignancies (Study CRSP-ONC-001; ClinicalTrials.gov identifier NCT04035434) are summarized in Section 1.8 and Section 5.3.1.1.

1.6. CRISPR Technology

CRISPR (clustered regularly interspaced short palindromic repeats) are found in many bacteria and archaea flanking foreign DNA sequences. CRISPR are an important part of an adaptive bacterial defense system using RNA-guided DNA-cleaving enzymes (Barrangou et al., 2007; Hale et al., 2009). The RNAs expressed from CRISPR sequences direct the sequence-specific binding of CRISPR-associated protein 9 (Cas9) proteins. These key bacterial defense systems were adapted as a programmable RNA-directed CRISPR-Cas9 system for editing genomes (Jinek et al., 2012).

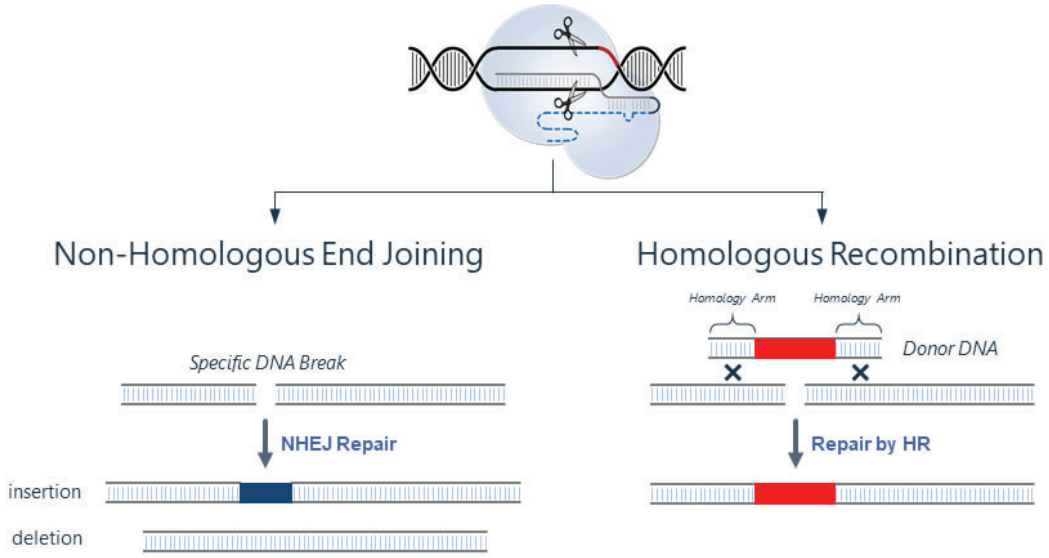
CRISPR-Cas9 systems can be directed by a complex of 2 distinct RNAs: crisprRNA (crRNA) and trans-activating crRNA (tracrRNA), or by a single-guide RNA (sgRNA) containing the crRNA and tracrRNA joined by a loop (Jinek et al., 2012). Delivery of Cas9 nuclease and sgRNA into a cell results in cutting the cell's genomic DNA at sequences specified by the sgRNA 5' sequence (Figure 1) and leaving double-stranded breaks (DSBs). These DSBs are repaired by the cell's own DNA repair machinery. Repair of DSBs by the cellular nonhomologous end-joining (NHEJ) pathway often results in insertions or deletions, which lead to gene disruptions and knockouts. Alternatively, when donor DNA is supplied, DSBs can be repaired by a process of homology-directed repair (HDR) in which the donor DNA sequence is used to replace the genomic DNA sequence spanning the site of the DSB (Figure 2). HDR results in precise modification of the genomic sequence and can be used to correct mutations or introduce novel sequences at specific sites.

Figure 1: Schematic of the CRISPR-Cas9 Complex



A CRISPR-Cas9 complex containing an sgRNA wherein the crRNA and tracrRNA are joined by a linker loop.
Cas9: CRISPR-associated protein 9; CRISPR: clustered regularly interspaced short palindromic repeats; crRNA: crispr RNA; PAM: protospacer-adjacent motif; sgRNA: single-guide RNA; tracrRNA: trans-activating crRNA.

Figure 2: CRISPR-Cas9–Mediated Genome Editing Strategies



CRISPR-Cas9–mediated DNA cleavage creates a DSB at the target locus that is repaired either by the cells' NHEJ or HDR (denoted in the figure as Homologous Recombination) pathways. Once the sgRNA/Cas9 nuclease complex is bound to DNA at a target site, 2 independent nuclease domains in Cas9 (shown as scissors) each cleave 1 of the DNA strands 3 bases upstream of the protospacer-adjacent motif site, leaving a blunt-end DNA DSB. Formation of the site-specific DSB is the first key step in genome editing, followed by cellular repair.
Cas9: CRISPR-associated protein 9; CRISPR: clustered regularly interspaced short palindromic repeats; DSB: double-stranded break; HDR or HR: homology-directed repair; NHEJ: nonhomologous end-joining; sgRNA: single-guide RNA.

Target sites for CRISPR-Cas9 systems are distributed throughout the genome. The only requirement is that the target sequence, homologous to the 5' end of the sgRNA, is followed by a protospacer-adjacent motif (PAM) sequence (Horvath et al., 2008; Mojica et al., 2009; Shah et al., 2013). For *Streptococcus pyogenes* Cas9, this is any nucleotide followed by a pair of

guanines (marked as NGG). Typically, the specificity-determining region of the sgRNA is 20 nucleotides in length.

The Cas9 nuclease searches for the PAM site and adjacent sequence matching the sgRNA 5' end before cleaving the DNA. Therefore, target-site specificity results from a required combination of the site matching the sgRNA adjacent to a PAM site. The Cas9 nuclease does not bind to sequences without being complexed to a matching sgRNA. The Cas9 nuclease and sgRNA will not bind or cut unless the target sequence is adjacent to the PAM.

Multiple guide sequences can be targeted to enable simultaneous or sequential editing of different sites within the genome (Cong et al., 2013). The resulting multiplex editing can employ different editing methods, such as NHEJ at one site(s) and HDR at another site(s) (González et al., 2014). CRISPR systems therefore present a very promising means of creating multiple sets of complex edits.

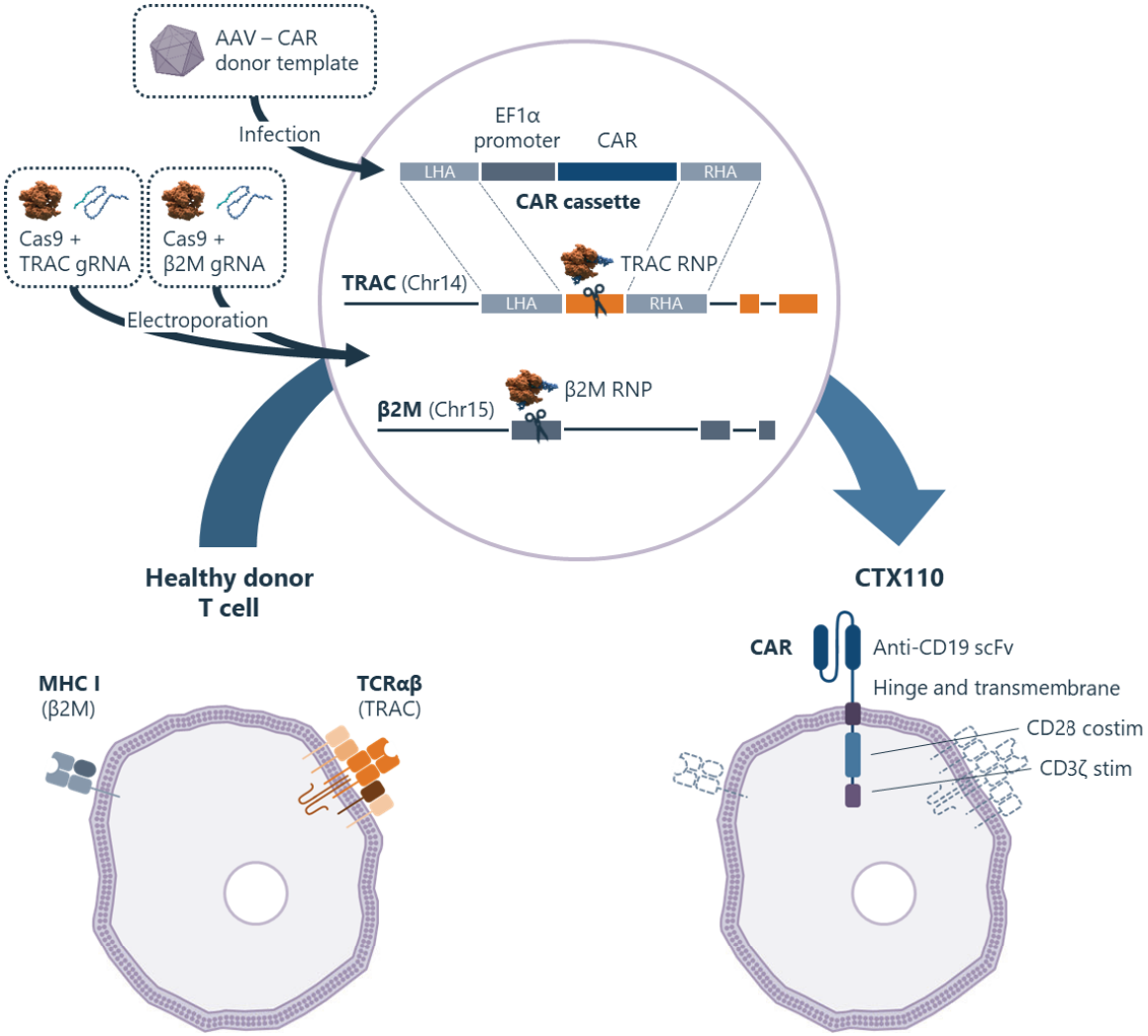
1.7. CTX110

CTX110 is a CD19-directed T cell immunotherapy comprised of allogeneic T cells that are genetically modified ex vivo using CRISPR-Cas9 gene editing components (guide RNA and Cas9 nuclease). The modifications include disruption of the T cell receptor alpha constant and beta-2 microglobulin (B2M) loci, and the simultaneous insertion of an anti-CD19 CAR transgene into the TRAC locus. The CAR is comprised of a murine scFv specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for CD28 and CD3 ζ. The gene knockouts are intended to reduce the probability of GvHD, redirect the modified T cells towards CD19-expressing tumor cells, and increase the persistence of the allogeneic cells.

The drug product is prepared from healthy donor peripheral blood mononuclear cells (PBMCs) obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and activated with anti-CD3/CD28 antibody–coated beads, then electroporated with CRISPR-Cas9 ribonucleoprotein complexes, and transduced with a CAR gene–containing recombinant adeno-associated virus (AAV) vector. The modified T cells are expanded in cell culture, purified, formulated into a [redacted] and [redacted] The product will be stored onsite and thawed immediately prior to administration.

A summary of CTX110 production is depicted in Figure 3. Nonclinical data supporting the clinical use of CTX110 are summarized in the Investigator Brochure.

Figure 3: Schematic of CTX110 Production



CTX110 is an allogeneic CRISPR-Cas9–edited T cell product that uses Cas9 nuclease protein and 2 guide RNAs for gene editing. The first guide RNA targets the TRAC locus (encoding the TCR) to direct homology-directed repair mechanisms to insert an anti-CD19 CAR expression cassette (delivered via a recombinant AAV vector) into the TRAC locus and disrupt the TCR. Disruption of the TCR is intended to minimize the probability of GvHD when the allogeneic T cell product is delivered into patients. The second guide RNA targets the B2M locus for disruption by nonhomologous end-joining. Disruption of the B2M (a component of MHC class I molecules) is intended to minimize the host's immune rejection of the allogeneic T cell product mediated by the MHC molecules when the allogeneic T cell product is delivered into patients, and thus improve persistence of CTX110 following dosing. Both guide RNAs and Cas9 nuclease protein are delivered by electroporation.
AAV: adeno-associated virus; β2M/B2M: beta-2 microglobulin; CAR: chimeric antigen receptor; Cas9: CRISPR-associated protein 9; Chr: chromosome; CRISPR: clustered regularly interspaced short palindromic repeats; EF1α: elongation factor 1 alpha; gRNA/sgRNA: guide RNA/single-guide RNA; LHA: left homology arm; MHC: major histocompatibility complex; RHA: right homology arm; RNP: ribonucleoprotein; scFv: single-chain variable fragment; TCR: T cell receptor; TCRαβ: T cell receptor alpha and beta chain complex; TRAC: T cell receptor alpha constant.

1.8. Study Rationale

Outcomes for patients with relapsed/refractory B cell malignancies are historically poor. However, the use of autologous CAR T cell therapy in this setting has produced complete and durable responses where previous treatment options were palliative (June et al., 2018; Maus and June, 2016; Neelapu et al., 2017; Schuster et al., 2019; Schuster et al., 2017). Autologous CAR T cell therapies require patient-specific cell collection and manufacturing. Unfortunately, some patients are not candidates to undergo leukapheresis, or they experience disease progression or death while awaiting treatment. An allogeneic off-the-shelf CAR T cell product such as CTX110 could provide the benefit of immediate availability, reduce manufacturing variability, and prevent individual subject manufacturing failures.

Further, patients treated with multiple rounds of chemotherapy may have T cells with exhausted or senescent phenotypes. The low response rates in patients with CLL treated with autologous CAR T cell therapy have been partially attributed to the exhausted T cell phenotype (Fraietta et al., 2018; Riches et al., 2013). By starting with chemotherapy-naïve T cells from a healthy donor, allogeneic approaches could increase the consistency and potency of CAR T therapy as compared to autologous products. This could lead to improved efficacy and facilitate the identification of biomarkers that predict clinical benefit.

The main barrier to the use of allogeneic CAR T cells has been the risk of GvHD. CRISPR-Cas9 gene-editing technology allows for reliable multiplex cellular editing. The CTX110 manufacturing process couples the introduction of the CAR construct to the disruption of the TRAC locus through homologous recombination. The delivery and precise insertion of the CAR at the TRAC genomic locus using an AAV-delivered DNA donor template and HDR contrasts with the random insertion of genetic material using lentiviral and retroviral transduction methods. CAR gene insertion at the TRAC locus results in elimination of TCR in nearly all cells expressing the CAR, which minimizes risk of GvHD. Furthermore, manufacturing from healthy donor cells removes the risk of unintentionally transducing malignant B cells (Ruella et al., 2018).

This first-in-human trial in subjects with relapsed/refractory B cell malignancies aims to evaluate the safety as well as efficacy of CTX110 with this CRISPR-Cas9–modified allogeneic CAR T cell approach. Refer to CTX110 Investigator's Brochure for the details of the preliminary safety data from Part A of the study.

The preliminary clinical safety data with CTX110 are largely consistent with other CD19-directed CAR T cell therapies. As of 10 April 2022 (the data cutoff date for CTX110 Investigator's Brochure Version 6.0), there have been no events of GvHD among 61 subjects who had received CTX110 in Phase 1, including 42 subjects with NHL (Cohort A [inclusive of legacy Cohort F] and Cohort C) and 6 subjects with adult B cell ALL (Cohort D) in Part A (dose escalation) and 13 subjects with NHL in Part B (expansion of the Cohort A regimen). Preliminary study data have shown that the treatment-emergent adverse events (TEAEs) observed are consistent with the underlying disease condition of lymphoma or LD chemotherapy. CTX110-related AEs are consistent with known pharmacological class effects of CAR T cell therapies and include CRS and immune effector cell–associated neurotoxicity syndrome (ICANS), and hematologic events. All cases of CRS resolved with supportive care, tocilizumab, and/or steroids, including 2 events of grade 3 CRS that occurred in 1 subject in

Part B Cohort A (1 event after a first CTX110 infusion and 1 after a second CTX110 infusion), both of which resolved within 6 days of onset. Four subjects had events of ICANS (3 subjects in Part A Cohort A and 1 subject in Part A Cohort C), including 1 event of serious grade 5 ICANS and human herpesvirus 6 (HHV-6) encephalitis with the outcome of death in 1 subject in Cohort A DL4 (1 DLT), and 1 subject with ICANS that started as grade 1 on Day 5 and worsened to grade 4, with subsequent recovery to grade 1 on Day 10 followed by resolution on Day 12. In Part A Cohort D, 1 subject had an SAE assessed as related to CTX110, a grade 2 infusion related reaction that occurred during CTX110 administration. No events of other AESIs specified in the study protocol, such as tumor lysis syndrome, B cell aplasia, secondary malignancy, or uncontrolled T cell proliferation, were reported in either part of the study (Phase 1 Part A and Part B) as of the data cutoff date.

The preliminary data with CTX110 from Part A of the clinical study also demonstrate the safety of a second CTX110 infusion. Eighteen subjects with NHL received a second infusion of CTX110, 9 of whom received the second infusion as part of the first course of treatment and 9 of whom received a second course of treatment. The occurrence and severity of AESIs was similar after first vs second infusion and no DLTs were reported in subjects who received a second CTX110 infusion. See Section 5.3.1.1 that supports the rationale for additional CTX110 infusions within the first course of treatment.

2. STUDY OBJECTIVES

Phase 1

Primary objective, Part A (dose escalation): To assess the safety of escalating doses of CTX110 in combination with various lymphodepletion agents in subjects with relapsed or refractory B cell malignancies to determine the recommended Part B or Phase 2 dose and cohort

Primary objective, Part B (cohort expansion): To assess the preliminary efficacy of CTX110 in subjects with relapsed or refractory B cell malignancies, as measured by objective response rate

Secondary objectives (dose escalation and cohort expansion):

- To further characterize the efficacy, safety, and PK of CTX110
- To evaluate the changes over time in patient-reported outcomes (PROs) associated with CTX110

Exploratory objectives [redacted]

[redacted]

Phase 2

Primary objective: To assess the efficacy of CTX110 in subjects with select NHL subtypes, as measured by objective response rate (ORR)

Secondary objectives:

- To further characterize the efficacy, safety, and pharmacokinetics (PK) of CTX110

- To evaluate the changes over time in patient-reported outcomes (PROs) associated with CTX110

Exploratory objectives: [redacted]

3. SUBJECT ELIGIBILITY

The eligibility criteria below are for enrollment in the study. Eligibility criteria for a second CTX110 infusion are provided in Section 5.3.1.3, and eligibility criteria for a second course of treatment after disease progression are provided in Section 5.3.1.4.

3.1. Inclusion Criteria

To be considered eligible to participate in this study, a subject must meet all the inclusion criteria listed below, which apply to all cohorts in Phase 1 and for subjects with NHL in Phase 2 unless otherwise specified.

1. Age ≥18 years (Phase 1 Cohorts A, B, and C and Phase 2), or ≥18 to ≤70 years (Phase 1 Cohort D)
2. Able to understand and comply with protocol-required study procedures and voluntarily sign a written informed consent document
3. Diagnosed with 1 of the following B cell malignancies:

   Phase 1 Cohorts A, B, and C (C1 and C2) and Phase 2: Histologically confirmed B cell NHLs: DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, transformed FL, grade 3b FL, or PMBCL

   - Confirmation of tumor histology from local pathology lab (archival tissue from last relapse/progression [within 3 months of enrollment] or biopsy during screening [or within 28 days prior to CTX110 infusion, if a recent sample was collected as part of standard of care])
   - At least 1 measurable lesion that is fluorodeoxyglucose positron emission tomography (PET)–positive, as defined by Lugano criteria (Deauville score of 4 or 5 on Lugano criteria 5-point scale; Appendix A). Note: Previously irradiated lesions will be considered measurable only if progression is documented following completion of radiation therapy.

   Phase 1 Cohort D: Histologically confirmed B cell ALL

   - Subcohort D1: Bone marrow involvement with ≥5% blasts (see investigational plan in Section 4.1).
   - Subcohort D2: Bone marrow MRD-positive (defined as $>1 \times 10^{-4}$ cells detected by flow cytometry or polymerase chain reaction [PCR] or next-generation sequencing [NGS] including ClonoSeq or positive BCR-ABL transcript for Ph+ disease) in subjects with bone marrow with ≤5% blasts. Subjects in Subcohort D2 may be enrolled with local baseline MRD results pending, as long as qualifying results within 3 months of enrollment are available.
4. Refractory or relapsed disease, as evidenced by the following cohort-specific criteria:

   Phase 1 Cohorts A, B, and C (NHL) and Phase 2 (NHL): 2 or more prior therapies, including an anti-CD20 monoclonal antibody and an anthracycline-containing regimen. Subjects who have received [redacted] must have recovered from [redacted] toxicities.

- Refractory disease is defined as subjects with PD on last therapy or have stable disease (SD) following at least 2 cycles of therapy.
- For subjects with transformed FL, subjects must have received at least 1 line of chemotherapy for disease after transformation to DLBCL.

- For **Phase 1 Cohort B**, subjects must meet the following criteria:
  - Received prior treatment with an approved autologous CD19-directed CAR T cell therapy (e.g., axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) ≥12 months prior to enrollment
  - Achieved a CR for ≥4 months duration from that prior treatment.
  - No grade ≥2 ICANS from prior CAR T cell therapy
  - No history of grade 4 CRS
  - No other prior or residual toxicity from prior CAR T cell therapy that, in the investigator's judgement, would place subject at increased risk of toxicity from a subsequent CAR T cell therapy
  - Age <70 years old
  - No elevated lactate dehydrogenase (LDH) (per institutional normal range)

  Note: Subjects with relapse after autologous CAR T cell therapy <6 months and/or 6 to 12 months prior to enrollment, those with elevated LDH, and those >70 years old may be considered after SRC review of safety and efficacy data from at least 6 subjects in Cohort B.

Phase 1 Cohort D (adult B cell ALL):

- 2 or more prior therapies, or
- Any bone marrow relapse after allogeneic HSCT; or
- Philadelphia chromosome–positive if subjects are intolerant to or ineligible for tyrosine kinase inhibitor (TKI) therapy or have progressed after at least 1 line of TKI therapy

5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Appendix B)
6. Meets criteria to undergo LD chemotherapy (all Phase 1 cohorts and Phase 2), CAR T cell infusion (all Phase 1 cohorts and Phase 2), and daratumumab administration (Phase 1 Cohort C only)
7. Adequate organ function:
   - Renal: Estimated glomerular filtration rate >50 mL/min/1.73 m^2
   - Liver: Aspartate transaminase (AST) or alanine transaminase (ALT) <3 × upper limit of normal (ULN); total bilirubin <1.5 × ULN (for subjects with Gilbert's syndrome, total bilirubin <2 mg/dL)

- Cardiac: Hemodynamically stable and left ventricular ejection fraction ≥45% by echocardiogram
- Pulmonary: Oxygen saturation level on room air >91% per pulse oximetry

8. Female subjects of childbearing potential (postmenarcheal with an intact uterus and at least 1 ovary, who are less than 1 year postmenopausal) must agree to use acceptable method(s) of contraception from enrollment through at least 12 months after the most recent CTX110 infusion (Appendix C).
9. Male subjects must agree to use effective acceptable method(s) of contraception from enrollment through at least 12 months after the most recent CTX110 infusion (Appendix C).

3.2. Exclusion Criteria

To be eligible for entry into the study, the subject must not meet any of the exclusion criteria listed below, which apply to all cohorts in Phase 1 and for subjects with NHL in Phase 2 unless otherwise specified.

1. Treatment with the following therapies as described below:
   - Prior treatment with any gene therapy or genetically modified cell therapy, including CAR T cells. Exception: Phase 1 Cohort B will enroll subjects who received prior treatment with an approved autologous CD19-directed CAR T cell therapy.
   - Prior treatment with a CD19-directed therapy (e.g., CD19-directed antibody, bispecific T cell engager, or antibody-drug conjugate, unless there is confirmed CD19 expression (by immunohistochemistry or flow cytometry) after progression or relapse following most recent CD19-directed treatment. The requirement to confirm CD19 expression is optional in Phase 1 Subcohort D2. Subjects in Phase 1 Cohort B should demonstrate confirmed CD19 expression.
2. Prior allogeneic HSCT. Exception: For subjects with B cell ALL (Phase 1 Cohort D), prior allogeneic HSCT is permissible if it has been more than 6 months from HSCT at the time of enrollment; there is no evidence of acute or chronic GvHD; and the subject has recovered from HSCT-related toxicities, has been off immunosuppressive therapies for at least 3 months prior to enrollment, and has not received donor lymphocyte infusion for at least 2 months prior to enrollment.
3. Diagnosis of Burkitt's lymphoma/leukemia
4. Known contraindication to daratumumab (Phase 1 Cohort C only), cyclophosphamide, fludarabine, or any of the excipients of CTX110 product
5. Prior CNS disease
   - For NHL subjects: Detectable malignant cells from CSF or magnetic resonance imaging (MRI) indicating brain metastases during screening, or a history of central nervous system (CNS) involvement by malignancy (CSF or imaging).
   - For B cell ALL subjects: a prior history of CNS involvement with no evidence of current CNS disease during screening and/or those with CNS-2 disease, which is

defined as the presence of blast cells in CSF containing <5 white blood cells/µl per National Comprehensive Cancer Network (NCCN) guidelines V2.2021 (NCCN, 2021), without neurological symptoms are eligible for the study. The SRC will review the first 2 subjects with CNS-2 ALL to allow additional subjects with CNS disease to be enrolled.

6. History of a seizure disorder, major cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
7. Unstable angina, clinically significant arrhythmia, or myocardial infarction within 6 months of enrollment, or grade 3 or higher pericardial effusion at the time of enrollment
8. Presence of active bacterial, viral, or fungal infection that is uncontrolled, based on investigator judgment in consultation with the medical monitor
9. Positive for presence of human immunodeficiency virus (HIV) type 1 or 2, or active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Subjects with prior history of HBV or HCV infection who have documented undetectable viral load (by quantitative PCR or nucleic acid testing) are permitted. Infectious disease testing (HIV-1, HIV-2, HCV antibody and PCR, HBV surface antigen, HBV surface antibody, HBV core antibody) performed within 45 days of enrollment may be considered for subject eligibility
10. Previous or concurrent malignancy, except basal cell or squamous cell skin carcinoma, adequately resected and in situ carcinoma of cervix, or a previous malignancy that was completely resected and has been in remission for ≥5 years of enrollment.
11. Radiation therapy within 14 days of enrollment
12. For Phase 1 Cohorts A, B, and C (NHL) and Phase 2 (NHL): Use of systemic antitumor therapy or investigational agent within 14 days or 5 half-lives, whichever is longer, of CTX110 infusion. Exceptions: 1) prior inhibitory/stimulatory immune checkpoint molecule therapy, which is prohibited within 3 half-lives of CTX110 infusion; and 2) rituximab, other anti-CD20 monoclonal antibodies, or polatuzumab vedotin use within 30 days prior to CTX110 infusion is prohibited (however PET/CT needs to occur at least 2 weeks after last dose).

    For Phase 1 Cohort D (adult B cell ALL): Use of systemic antitumor therapy within 7 days of CTX110 infusion. Exceptions: 1) immunotherapy agents (i.e., rituximab, inotuzumab) must be stopped at least 14 days prior to CTX110 infusion; 2) long-acting chemotherapy agents (e.g., pegylated asparaginase, methotrexate >25 mg/m^2) must be stopped at least 14 days prior to CTX110 infusion; 3) Hydroxyurea must be stopped ≥72 hours before CTX110 infusion; and 4) investigational agent(s) must be stopped after 5 half-lives have passed before CTX110 infusion. Subjects must have recovered to grade 1 Common Terminology Criteria for Adverse Events (CTCAE; National Cancer Institute, version 5.0) from acute toxicity (except hematological) of all previous therapy prior to CTX110 infusion. 5) Steroids are permitted until the day before starting LD chemotherapy for maintenance or to allow for control of peripheral blood blasts.
13. Primary immunodeficiency disorder or active autoimmune disease requiring steroids and/or other immunosuppressive therapy.

14. Diagnosis of significant psychiatric disorder or other medical condition that, in the opinion of the investigator, could impede the subject's ability to participate in the study
15. Women who are pregnant or breastfeeding
16. Life expectancy of less than 6 weeks
17. For Phase 1 Subcohort D2 only: Exclusion of isolated extramedullary disease (defined as any subject with ≤5% blasts in the bone marrow and confirmation of the presence of clonal blasts in any tissue other than the medullary compartments)

4. STUDY DESIGN

This is an open-label, multicenter, Phase 1/2 study evaluating the safety and efficacy of CTX110 in subjects with relapsed or refractory B cell malignancies. Phase 1 of the study will be divided into 2 parts: dose escalation (Part A) followed by cohort expansion (Part B). Phase 2 will further explore efficacy in cohorts that have been evaluated in Phase 1.

4.1. Phase 1 Investigational Plan

In Phase 1, dose escalation (Part A) and cohort expansion (Part B) will be conducted separately for each cohort and performed according to the criteria outlined in Section 4.1.4. An SRC, consisting of investigators and sponsor representatives, will review all available safety data and make decisions regarding dose escalation (or de-escalation), additional CTX110 infusion, LD chemotherapy dose regimen, and daratumumab (Darzalex®, Janssen) dose regimen to determine the recommended Part B dose for cohort expansion and/or the recommended Phase 2 dose. The SRC may also propose revisions to the DLT definitions and dosing schema during dose escalation.

The study is designed to enroll adult subjects with 1 of the following NHL subtypes: DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, grade 3b FL, transformed FL, or PMBCL (Cohorts A, B, and C); and subjects with adult B cell ALL (Cohort D). Cohorts C and D are divided into Subcohorts C1 and C2 and D1 and D2, respectively. See Table 3 for CTX110, LD chemotherapy, and daratumumab (if applicable) dose regimens for each cohort.

Cohort B will enroll subjects with NHL who have achieved a CR on prior approved autologous CD19-directed CAR T cell therapy and subsequently experienced disease progression. The dose regimen will be the same as for Cohort A, and LD chemotherapy will comprise co-administration of fludarabine 30 mg/m^2 and cyclophosphamide 750 mg/m^2 IV daily for 3 days. The higher dose of cyclophosphamide is intended to improve peak cell expansion and persistence in this pre-treated population (Section 5.2.1). Initially, enrollment will be restricted to subjects who are ≥12 months from prior CAR T cell therapy, are age <70 years old, and have LDH in the normal range. However, after at least 6 subjects have been treated in Cohort B, the SRC may review of safety and efficacy data and determine that a broader population of post autologous CAR T cell therapy subjects may be enrolled.

To provide immunomodulatory effects to induce an immune environment amenable to allogeneic CAR T cells, subjects in Cohort C will receive daratumumab with or without LD chemotherapy (see Table 3). [redacted]

This study will allow for up to 3 infusions of CTX110 for each subject.

For all cohorts (except Subcohort C1), a second infusion of CTX110 with the respective LD regimen will be administered on Day 35 (-7 days/+21 days) to subjects who achieve SD or better at the Day 28 evaluation (Table 3). This additional infusion of CTX110 may be administered

without LD chemotherapy if a subject is experiencing significant cytopenias, as described in Section 5.3.1.3.

As shown in the STUDY SCHEMA and Table 3, the ***first course of treatment*** encompasses the initial CTX110 infusion with respective LD regimen and the second infusion with LD regimen, if applicable.

For all cohorts, if the subject has demonstrated clinical benefit after the initial CTX110 infusion but then has disease progression, an optional ***second course of treatment*** with a single infusion of CTX110 after PD will be administered ***with*** standard LD chemotherapy (i.e., without daratumumab for subjects in Phase 1 Cohort C) within 18 months of the initial CTX110 infusion and ≥4 weeks from the prior CTX110 infusion. See Table 3 for additional details regarding all Part A cohorts.

In Phase 1 Part A, for cases in which a dose level has been cleared in a cohort and dose escalation is permitted, the sponsor, in consultation with the SRC, may decide to enroll additional subjects at a given dose level. In any dose escalation cohort or subcohort (e.g., D1, or D2), 6 additional subjects (up to 12 total subjects) may receive study treatment at or below the highest cleared dose level. Further, with SRC approval, 12 additional subjects (24 total) may receive study treatment in any one cohort or subcohort (A, B, C1, C2, D1, or D2) at or below the highest cleared dose level to gather additional safety information prior to cohort expansion. Dose escalation for other cohorts may continue in parallel to cohort expansion and Phase 2 enrollment. Dose escalation for subjects with adult B cell ALL is anticipated to continue in parallel to cohort expansion and Phase 2 enrollment for NHL cohorts.

Table 3: Lymphodepletion Regimen and CTX110 Infusion Schedule (Part A Dose Cohorts)

Cohort	Disease Subtype	First Course of Treatment
A	NHL: Adult subjects with DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, grade 3b FL, transformed FL, or PMBCL	**Stage 2A** LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + **cyclophosphamide 500 mg/m^2** IV daily for 3 days; both agents should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion. **Stage 2B** • Initial CTX110 infusion on Day 1 starting at DL1 • A second infusion of CTX110 on Day 35 (-7 days/+21 days) administered with LD chemotherapy for subjects who achieve SD or better at Day 28 scan (based on Lugano criteria).
B*	Same as Cohort A, with additional inclusion criteria related to prior autologous CAR T cell therapy	**Stage 2A** LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + **cyclophosphamide 750 mg/m^2** IV daily for 3 days; both agents should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion. **Stage 2B** • Initial CTX110 infusion on Day 1 starting at DL4 • A second infusion of CTX110 on Day 35 (-7 days/+21 days) with LD chemotherapy (co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days) to subjects who achieve SD or better at Day 28 scan (based on Lugano criteria).
C (Subcohorts C1 and C2)	Same as Cohort A	**Stage 2A** LD regimen: Daratumumab + LD chemotherapy Daratumumab administration: One dose of daratumumab[1] 16 mg/kg by IV infusion or 1800 mg by SC injection ≥1 day prior to starting LD chemotherapy and within 10 days prior to CTX110 infusion. To facilitate administration, the first 16 mg/kg IV dose may be split (to 8 mg/kg) over 2 consecutive days. LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + **cyclophosphamide 500 mg/m^2** IV daily for 3 days; both agents should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion. **Stage 2B** Cohort C1 • Initial CTX110 infusion on Day 1 starting at DL3 • No second infusion of CTX110 on Day 35 • For subjects who achieve SD or better on Day 28, 2 additional doses of daratumumab (16 mg/kg by IV infusion or 1800 mg by SC injection) will be administered at Day 28 (± 4 days) and Month 2 (± 4 days) visits.

Cohort	Disease Subtype	First Course of Treatment
		Cohort C2 • Initial CTX110 infusion on Day 1 starting at or below the DL cleared in Cohort C1 • A second infusion of CTX110 on Day 35 (-7 days/+21 days) administered with daratumumab[2] and LD chemotherapy to subjects who achieve SD or better at Day 28 scan (based on Lugano criteria).
D (Subcohorts D1 and D2)	Adult B cell ALL D1: BM involvement with ≥5% blasts. D2: BM <5% blasts and MRD-positive (>1 × 10-4 cells detected by flow cytometry or PCR or NGS including ClonoSEQ or positive BCR-ABL transcript for Ph+ disease).	**Stage 2A** LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + **cyclophosphamide 500 mg/m^2** IV daily for 3 days; both agents should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion.[3] **Stage 2B** Cohort D1 (BM involvement with ≥5% blasts) • Initial CTX110 infusion on Day 1 starting at DL2 or DL3 • A second infusion of CTX110 on Day 35 (-7 days/+21 days) with LD chemotherapy if subject has a decrease in BM blast count at Day 28 of ≥50% but blast count remains ≥5% or is MRD-positive. Cohort D2 (BM involvement with <5% blasts and MRD-positive) • CTX110 infusion on Day 1 starting at or below the DL cleared in D1 • Second infusion of CTX110 on Day 35 for subjects who have demonstrated a reduction in detectable MRD and remain MRD positive.

ALL: acute lymphoblastic leukemia; BM: bone marrow; CAR: chimeric antigen receptor; DL: Dose Level; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; IV: intravenous(ly); LD: lymphodepleting; MRD: minimal residual disease; NGS: next-generation sequencing; NHL: Non-Hodgkin Lymphoma; NOS: not otherwise specified; PCR: polymerase chain reaction; PMBCL: primary mediastinal large B cell lymphoma; SC: subcutaneous; SD: stable disease.

Note: Subjects in legacy Cohort F (discontinued in Version 6.0 of the protocol) have been merged with Cohort A.

Note: Subjects should meet the criteria specified in the protocol prior to both the initiation of LD chemotherapy and infusion of CTX110 and should meet criteria specified for second or subsequent infusions prior to receiving any additional doses of CTX110. Criteria for LD chemotherapy should be confirmed prior to infusion of daratumumab as applicable. The CTX110 infusion on Day 35 (-7 days/+21 days), if applicable, may be administered without LD chemotherapy if subject is experiencing significant cytopenias (see Section 5.3.1.3.1).

Subjects in all cohorts have the option to receive an additional infusion of CTX110 with LD chemotherapy (co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days) after PD, as a second course of treatment, if subjects had response after prior infusion. Additional infusion after PD must be within 18 months of the initial CTX110 infusion and ≥4 weeks after last infusion.

* Cohort B will enroll subjects only at selected investigative sites, at the sponsor's discretion.

1. Daratumumab may be administered as an SC injection (1800 mg/30,000 units of hyaluronidase-fihj) or as an IV infusion of 16 mg/kg, per local prescribing information.
2. For subjects in Cohort C2 who respond to treatment (i.e., achieve SD or better on Day 28), an additional dose of daratumumab will be administered at the Day 28 visit and an additional infusion of CTX110 will be administered on Day 35. A second additional daratumumab dose will be administered as part of the LD regimen for Day 35 unless within 14 days of the previous Day 28 dose (Section 5.1).
3. In Cohort D, additional subjects may be enrolled to explore alternative LD dose regimen in which cyclophosphamide may be administered at a dose of 750 mg/m^2 IV daily for 3 days, starting at a CTX110 dose

level at or below the highest dose level that has been cleared with LD dose containing 500 mg/m^2 IV daily for 3 days and if it has been agreed by the SRC and the sponsor. Additional subjects enrolled will follow dose escalation rules as described in Section 4.1.4. In that instance, for the second infusion on Day 35 (where applicable), the cyclophosphamide dose in LD chemotherapy will be 500 mg/m^2.

4.1.1. Phase 1 Study Design

The study will consist of 3 main stages: screening, treatment, and follow-up. The dose escalation part of the study will involve 4 cohorts of subjects: Cohorts A, B, C, and D. Cohorts C and D include Subcohorts C1 and C2 and D1 and D2, respectively.

Enrollment and allocation of subjects to each cohort will be at the sponsor's discretion. Subjects with B cell ALL will be exclusively assigned to Cohort D in parallel with other cohorts.

The 3 main stages of the study will be as follows:

Stage 1 – Screening to determine eligibility for treatment (1-2 weeks)

Stage 2 – Treatment (**Stage 2A** + **Stage 2 B**). See Table 3 for treatment by cohort.

Stage 3 – Follow-up for all cohorts (up to 5 years after the last CTX110 infusion)

Note: Subjects' clinical eligibility should be reconfirmed according to the criteria in Sections 5.2 and 5.3 prior to both the initiation of LD chemotherapy (all cohorts), infusion of CTX110 (all cohorts), and prior to administration of daratumumab (Cohort C).

Criteria for additional CTX110 infusions are described in Section 5.3.1.

For Phase 1 Part A (dose escalation), subjects must remain within proximity of the investigative site (i.e., 1-hour transit time) for 28 days after each CTX110 infusion. For Phase 1 Part B (cohort expansion), subjects must remain within proximity of the investigative site (i.e.,1-hour transit time) for 28 days after the first CTX110 infusion and at least 14 days for subsequent CTX110 infusions, or longer if justified by subject's clinical status or as required by local regulation or site practice. During this acute toxicity monitoring period, subjects will be routinely assessed for AEs, including CRS, neurotoxicity, and GvHD. Toxicity management guidelines are provided in Section 6. During dose escalation, all subjects will be hospitalized for the first 7 days following each CTX110 infusion, or longer if required by local regulation or site practice (Appendix D).

After the acute toxicity monitoring period, subjects will be subsequently followed for up to 5 years after the last CTX110 infusion with physical exams, regular laboratory and imaging assessments, and AE evaluations.

4.1.2. Phase 1 Study Subjects

Approximately 100 subjects will be treated in Part A (dose escalation), depending on which cohorts are enrolled and the number of dose levels explored.

Up to 30 subjects will be treated in Part B (cohort expansion) of Cohort A. If other cohorts expand, the sample size estimation for the first cohort expansion will also apply to the subsequent cohort expansion, thus increasing the total number of enrolled subjects in Part B.

Section 7.1.3 describes the assignment of subjects to treatment cohorts.

4.1.3. Phase 1 Study Duration

Subjects will participate in this study for up to 5 years after the last CTX110 infusion. All subjects will also be asked to participate in a separate long-term follow-up study for an additional 10 years to assess long-term safety and survival.

4.1.4. Phase 1 Part A Dose Escalation

In Phase 1 Part A, the following doses of CTX110, based on number of CAR^+ T cells, may be evaluated in this study (Table 4).

Table 4: Dose Escalation of CTX110

Dose Level	Total CAR^+ T Cell Dose
−1	1×10^7
1	3×10^7
2	1×10^8
3	3×10^8
3.5*	4.5×10^8
4	6×10^8
5**	9×10^8

CAR: chimeric antigen receptor; DL: Dose Level.
* DL3.5 is an optional de-escalation dose level.
**Note: The sponsor, with approval of the safety review committee, may explore DL5 (9×10^8 cells) in parallel to cohort expansion.

Dose escalation will be performed using a standard 3+3 design in which 3 to 6 subjects will be enrolled at each dose level depending on the occurrence of DLTs, as defined in Section 4.1.4.2. The SRC will review available data when the DLT observation period ends for the last subject enrolled in each cohort. The SRC will be responsible for making dose escalation decisions based on review of all available safety and PK data. Throughout dose escalation, for cases in which a dose had been cleared in a cohort or subcohort (e.g., Subcohort D1) and dose escalation is permitted, the sponsor in consultation with the SRC may alternatively decide to enroll an additional number of subjects for a total of up to 24 at the current dose level to gather additional safety data. Based on an ongoing assessment of benefit and risk, the SRC may stop dose escalation before a maximum tolerated dose (MTD) is determined.

The doses of CTX110 presented in Table 4, based on the total number of CAR^+ T cells, may be evaluated in this study. The starting dose for escalation will be selected separately for each cohort and will reflect the cumulative safety data across all cohorts for each study population (NHL, adult B cell ALL). Whenever escalation begins in a new cohort, the sponsor and SRC will discuss and agree on the starting dose level, which will not exceed the highest dose level cleared in Cohort A. There will be a dose limit of [redacted] TCR^+ cells/kg for all dose levels, which will determine the minimum weight for dosing.

The DLT evaluation period will begin with the initial CTX110 infusion and last for 28 days.

In addition to a formal assessment of DLTs following the first dose of CTX110, the sponsor will systematically review safety for each dosing regimen, including for subjects who receive:

1. Second infusion of CTX110 at Day 35 with or without LD chemotherapy (see Section 5.3.1.3)
2. Day 28 and Month 2 doses of daratumumab (Cohort C1) (see Section 5.1)
3. A second course of study treatment after disease progression (see Section 5.3.1.4)

Events that could be considered DLTs in any of these settings will be brought to the SRC for review and discussion. Further, the incidence and severity of long-term cytopenias will be monitored and summarized by dosing regimen, and subject to the same DLT definition as outlined in Section 4.1.4.2. The sponsor will collect and monitor AEs, SAEs, and adverse events of special interest (AESIs) per protocol and analyze safety information relative to the first dose and compare the safety information relative to the second dose for the subjects who receive additional infusions, in addition to the cumulative safety data analysis for subjects who receive single and additional infusions in each cohort. The sponsor will also continue to share and discuss with the SRC on a regular basis the safety profile of subjects who receive a single infusion of CTX110 and of subjects who have received additional infusions. These data will be reviewed on an ongoing basis by the DSMB. The sponsor will apply the DLT criteria defined in Section 4.1.4.2 to assess safety in addition to the frequency and severity of AEs and AESIs collected during the immediate 28-day period after each additional CTX110 infusion. The sponsor will discuss the results with the SRC after the first 3 subjects have received an additional infusion of CTX110 within each cohort, and at regular intervals as more subjects receive additional CTX110 infusions.

For Cohort A: In DL1 (and DL-1, if required), subjects will be treated in a staggered manner such that the second and third subjects will only receive CTX110 after the previous subject has completed the DLT evaluation period. In subsequent dose levels or for additional subjects enrolled at the same dose level, cohorts of up to 3 subjects may be enrolled and dosed concurrently.

For Cohorts B, C, and D: The first 2 subjects within each cohort will be treated in a staggered manner at the starting dose level and at each subsequent dose level, such that the second subject will only receive CTX110 after the previous subject has completed the DLT evaluation period. For additional subjects enrolled at the same dose level, cohorts of up to 3 subjects may be enrolled and dosed concurrently.

For Cohort D: The first 2 subjects at each dose level of Subcohort D1 (adult B cell ALL subjects with ≥5% blasts) will be treated in a staggered manner such that the second subject will only receive CTX110 after the previous subject has completed the DLT evaluation period. However, in Subcohort D2 (adult B cell ALL subjects with <5% blasts and MRD positive), up to 3 subjects may be enrolled and dosed concurrently if the dose level has been cleared by the SRC in Subcohort D1. The opposite will not be allowed. If 3 subjects in Subcohort D2 are cleared, then Subcohort D2 alone will advance to the next dose level.

The sponsor considers this approach to subject enrollment appropriate for this first-in-human study with CTX110, given that dose escalation will only be performed in centers with extensive

experience administering cell therapies, and the existence of comprehensive toxicity management algorithms based on CD19-directed autologous CAR T cell therapy (Section 6).

Dose escalation will be performed according to the following rules:

- If 0 of 3 subjects experience a DLT, escalate to the next dose level.
- If 1 of 3 subjects experiences a DLT, expand the current dose level to 6 subjects.
    - If 1 of 6 subjects experiences a DLT, escalate to the next dose level.
    - If ≥2 of 6 subjects experience a DLT:
        - For Cohort A, if in DL-1, evaluate alternative dosing schema or declare inability to determine recommended Part B dose.
        - For Cohort A, if in DL1, de-escalate to DL-1. For Cohort D, if in DL2, de-escalate to DL1.
        - For all cohorts, if in DL 2, 3, 3.5, 4, or 5 declare previous dose level the MTD.
- If ≥2 of 3 subjects experience a DLT:
    - For Cohort A, if in DL-1, evaluate alternative dosing schema or declare inability to determine recommended Part B dose.
    - For Cohort A, if in DL1, decrease to DL-1. For Cohort D, if in DL2, de-escalate to DL1.
    - For all cohorts, if in DL 2, 3, 3.5, 4, or 5 declare previous dose level the MTD.

The sponsor will declare the recommended dose for Part B cohort expansion or Phase 2 at or below the MTD (if determined). At least 6 subjects will be administered CTX110 in the trial before a recommended Part B dose is declared.

4.1.4.1. CTX110 Dose Rationale: Part A

Nonclinical safety models are limited in part because the CD19-directed CAR does not recognize murine CD19, and therefore these studies cannot evaluate CD19-dependent toxicities. Additionally, the PK profile of CTX110 cannot be evaluated in CD19 antigen–free mouse models, or in immunocompetent nonhuman primate models in which rapid clearance would be expected, as CTX110 is a human cell. Therefore, the starting dose of CTX110 is predominantly informed by published clinical studies of other autologous and allogeneic CD19-directed CAR T cell therapies (Table 5). In clinical trials, CAR T cells have been administered as 1 specific CAR^+ T cell dose or as per kilogram dosing, depending on the clinical trial and product.

Table 5: CAR^+ T Cell Doses

Product	Indication	Dosing (CAR^+ T cells)
Tisagenlecleucel	Pediatric/young adult ALL	Subjects >50 kg: Range of doses, maximum 2.5×10^8 Subjects <50 kg: $0.2\text{-}6.0 \times 10^6$

Product	Indication	Dosing (CAR^+ T cells)
Tisagenlecleucel	NHL	5×10^8
Axicabtagene ciloleucel	NHL	2×10^6/kg, maximum 2×10^8
Lisocabtagene maraleucel	NHL	$5 \times$x 10^7 and 1×10^8

ALL: acute lymphoblastic leukemia; CAR: chimeric antigen receptor; NHL: non-Hodgkin lymphoma.

CTX110 will be administered IV using a flat dosing schema based on the number of CAR^+ T cells. The starting dose will be 3×10^7 CAR^+ T cells, which is approximately 1 log lower than the doses of autologous CAR T cells currently approved for NHL, reflecting a conservative approach given this study is the first clinical experience with CTX110. Prior CAR T cell studies have failed to demonstrate a strong dose-response relationship for either safety or efficacy outcomes (Mueller et al., 2017). Some studies report ≤100,000-fold expansion of CAR T cells in subjects after infusion, resulting in highly variable systemic exposure to CAR T cells even at the same dose (Maude et al., 2015; Schuster et al., 2019; Schuster et al., 2017). Toxicities associated with autologous CAR T cells are likely due to several factors in addition to dose such as the malignancy being treated, disease status (including tumor burden) at the time of infusion, and, potentially, LD chemotherapy doses.

4.1.4.2. DLT Definitions

Toxicities will be graded and documented according to National Cancer Institute CTCAE version 5.0 (Appendix E), except as provided in Section 6.2.4 for CRS (American Society for Transplantation and Cellular Therapy [ASTCT] criteria (Lee et al., 2019), Section 6.2.5 for neurotoxicity (Lee et al., 2019), and Section 6.2.9 for GvHD (Harris et al., 2016).

A DLT will be defined as any of the following events occurring during the DLT evaluation period that persists beyond the specified duration (relative to the time of onset):

- Grade ≥2 GvHD that is steroid-refractory (e.g., PD after 3 days of steroid treatment [e.g., 1 mg/kg/day], SD after 7 days, or PR after 14 days of treatment)
- Death during the DLT period (except due to disease progression)
- Grade 4 neurotoxicity of any duration that is related or possibly related to CTX110
- Any CTX110-related grade 3 or 4 toxicity that is clinically significant according to the investigator's judgment and does not improve within 72 hours

The following will **NOT** be considered as DLTs:

- Grade 3 or 4 CRS that improves to grade ≤2 within 72 hours
- Grade 3 neurotoxicity (e.g., encephalopathy, confusion) that improves to grade ≤2 within 14 days
- Grade 3 or 4 fever
- Bleeding in the setting of thrombocytopenia (platelet count $<50 \times 10^9$/L); documented bacterial infections or fever in the setting of neutropenia (absolute neutrophil count [ANC] $<1000/mm^3$)

- Hypogammaglobulinemia
- Grade 3 or 4 pulmonary toxicity that resolves to grade ≤2 within 7 days. For subjects intubated due to fluid overload from supportive care, this may be extended to 14 days.
- Grade 3 or 4 liver function studies that improve to grade ≤2 within 14 days
- Grade 3 or 4 renal insufficiency that improves to grade ≤2 within 21 days
- Grade 3 or 4 thrombocytopenia, neutropenia, anemia, or lymphopenia will be assessed retrospectively. After at least 6 subjects are infused, if ≥50% of subjects have prolonged cytopenias (i.e., lasting more than 28 days post infusion) dose escalation will be suspended pending SRC review. For Cohort D: Grade ≥3 cytopenias that were present at the start of LD chemotherapy may not be considered a DLT pending SRC review and identification of another etiology.

Subjects must receive CTX110 to be evaluated for DLT. If a subject discontinues the study any time prior to the initial CTX110 infusion, the subject will not be evaluated for DLT and a replacement subject will be enrolled at the same dose level as the discontinued subject. If a subject has a potential DLT for which the protocol definition allows time for improvement or resolution, the DLT evaluation period will be extended accordingly before a DLT is declared. AEs occurring outside the DLT evaluation period that are assessed by the investigator and/or sponsor as related to CTX110 will be considered by the SRC when making dose escalation decisions. AEs that have no plausible causal relationship with CTX110 will not be considered DLTs. A DLT occurring in one cohort will not impact enrollment in another cohort unless the sponsor and SRC consider there is an increased overall safety risk.

4.1.4.3. Rationale for DLT Definitions

The DLT definitions used in this study are informed by prior experience with autologous CAR T cell therapies. The clinical data from tisagenlecleucel and axicabtagene ciloleucel in NHL (including DLBCL) indicate that although CAR T cell therapies can cause grade 3-4 toxicities in approximately 13-40% of subjects, most toxicities respond to treatment and resolve with no sequelae (Table 6).

Table 6: Frequency of Severe AEs Reported With Tisagenlecleucel and Axicabtagene Ciloleucel in Subjects With NHL

Adverse Event	Tisagenlecleucel[1]	Axicabtagene Ciloleucel[2]
Grade ≥3 cytokine release syndrome	Frequency: 23% Median duration: 8 days (range: 1-36)	Frequency: 13% Median duration: 7 days (range: 2-58)
Grade ≥3 neurological toxicities	Frequency: 18% Median duration: 14 days	Frequency: 31% Median duration: 17 days
Prolonged grade ≥3 cytopenias	At day 28 post infusion: 40% thrombocytopenia 25% neutropenia	At day 30 post infusion: 18% thrombocytopenia 15% neutropenia

[1.] From tisagenlecleucel package insert (Kymriah USPI, 2017).
[2.] From axicabtagene ciloleucel package insert (Yescarta USPI, 2017).

The sponsor, in consultation with participating investigators experienced in the administration of CAR T cell therapies, have developed protocol DLT definitions that allow time for select AEs to improve with appropriate medical management as well as reflect risks that are specific to an allogeneic product (e.g., GvHD; see Section 6.2.9). The protocol provides extensive guidance regarding how to identify and treat AEs that were previously seen with autologous CAR T cell therapies (Section 6). Subjects in Phase 1 Part A (dose escalation) will be hospitalized or remain in proximity of the investigative site (i.e., 1-hour transit time) for at least 28 days after each CTX110 infusion to ensure appropriate safety monitoring.

The SRC will closely monitor the evolving safety data from CTX110 during dose escalation, including potential DLTs that occur outside the DLT evaluation period, and may adjust the DLT criteria further with input from the DSMB.

The sponsor considers this approach appropriate to balance the principal goal of protecting subject safety while reducing the likelihood that dose escalation is stopped prematurely, thereby allowing adequate opportunity to demonstrate efficacy in a high-risk oncology population with limited treatment options.

4.1.5. Phase 1 Part B Cohort Expansion and Recommended Dose

Cohort expansion (Part B) will begin with Cohort A to further evaluate the safety and efficacy of CTX110 in NHL subjects. Cohort expansion can be performed for any cohorts that have completed dose escalation and for which the Part B dose has been determined per the protocol-specified criteria, with agreement from the SRC, DSMB, and at the sponsor's discretion. Alternatively, the sponsor, in agreement with the SRC and DSMB, may begin Phase 2 for any NHL cohort that has completed dose escalation (Section 4.2), after selection of a recommended Phase 2 dose.

Recommended Part B Dose Rationale (Cohort A)

As of 22 December 2021, the study had enrolled a total of 34 subjects in Cohort A (inclusive of legacy Cohort F in the global version of the protocol) and had completed dose escalation for Cohort A. Among the 34 enrolled subjects, 32 received CTX110 infusion. Three subjects were treated with CTX110 in DL1 (3×10^7 CAR^+ T cells), 3 in DL2 (1×10^8 CAR^+ T cells), 6 in DL3 (3×10^8 CAR^+ T cells), 6 in DL3.5 (4.5×10^8 CAR^+ T cells), and 14 in DL4 (6×10^8 CAR^+ T cells).

The selection of DL4 (6×10^8 CAR^+ T cells) as the recommended Part B dose for NHL subjects in Cohort A was based on preliminary efficacy results comparable to available autologous CAR T cell therapies, lack of DLTs, and an overall acceptable safety profile.

Based on the totality of safety and efficacy data obtained from these subjects, the sponsor in agreement with the SRC and an independent data safety monitor board (DSMB) has selected 6×10^8 CAR^+ T cells (DL4) as the recommended Part B dose for cohort expansion to further evaluate the safety and efficacy of CTX110 in NHL subjects. The dose regimen for expansion will be the same as for Part A Cohort A, as described in Table 3.

4.2. Phase 2 Investigational Plan

Following dose escalation of any Phase 1 cohort, the sponsor may begin enrollment in Phase 2 to evaluate efficacy and safety of CTX110 in a larger population of subjects. Enrollment to Phase 2 will be at the sponsor's discretion, with agreement from the SRC and DSMB.

Phase 2 will begin with subjects with NHL at the recommended dose and regimen determined in Phase 1 for Cohort A, to further evaluate the efficacy and safety of CTX110 in subjects with NHL (see Section 4.2.4). Approximately 97 subjects with NHL will be enrolled. Where required, regulatory approval will be obtained prior to enrolling any subjects from that region into Phase 2.

Phase 2 may be conducted in parallel with Phase 1 dose escalation or cohort expansion of other cohorts in the study.

One interim analysis is planned in Phase 2 for early efficacy and futility based on the total population of the expanded cohort for NHL and will be performed by an independent statistician and reviewed by the DSMB. This interim analysis will occur when 50% of the expected subjects in the total population have received CTX110 infusion and have 3 months of evaluable tumor response data or discontinued earlier. For Phase 2, a sample size of 97 subjects is planned.

4.2.1. Phase 2 Study Design

The study will consist of 3 main stages:

- **Screening** to determine eligibility for treatment (1-2 weeks)
- **Treatment**:
  - LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days; both agents should be started on the same day and administered for 3 consecutive days and completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion
  - Initial CTX110 infusion on Day 1 (6×10^8 CAR$^+$ T cells)
  - A second infusion of CTX110 (6×10^8 CAR$^+$ T cells) on Day 35 (-7 days/ +21 days) administered with LD chemotherapy for subjects who achieve SD or better at Day 28 scan (based on Lugano criteria). The second infusion may be administered without LD chemotherapy if the subject is experiencing significant cytopenias (see Section 5.3.1.3.1).
- **Follow-up** (up to 5 years after the last CTX110 infusion)

Each subject will have the option to receive an additional infusion of CTX110 with LD chemotherapy (co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days) after PD, as a second course of treatment, if the subject had response after the initial infusion. The additional infusion after PD must be within 18 months of the first CTX110 infusion and ≥4 weeks after the first infusion.

Subjects' clinical eligibility should be reconfirmed according to the criteria in Sections 5.2 and 5.3 prior to both the initiation of LD chemotherapy and infusion of CTX110, and according to the criteria in Section 5.3.1 for the second and any subsequent infusion of CTX110.

Subjects must remain within proximity of the investigative site (i.e., 1-hour transit time) for 28 days after the first CTX110 infusion and at least 14 days for subsequent CTX110 infusions, or longer if justified by the subject's clinical status, or required by local regulation or site practice. During this acute toxicity monitoring period, subjects will be routinely assessed for AEs, including CRS, neurotoxicity, and GvHD. Toxicity management guidelines are provided in Section 6.

After the acute toxicity monitoring period, subjects will be subsequently followed for up to 5 years after the last CTX110 infusion with physical exams, regular laboratory and imaging assessments, and AE evaluations.

4.2.2. Phase 2 Study Subjects

Approximately 97 subjects with NHL will be treated in Phase 2 with the Cohort A dose regimen, contingent upon the outcome of an interim analysis (Section 10.5).

4.2.3. Phase 2 Study Duration

As in Phase 1 (see Section 4.1.3), Phase 2 subjects will participate in this study for up to 5 years after the last CTX110 infusion. All subjects will also be asked to participate in a separate long-term follow-up study for an additional 10 years to assess long-term safety and survival.

4.2.4. Phase 2 Dose Rationale

Based on the acceptable safety profile of CTX110 and available clinical data from Part B for subjects with NHL, the recommended CTX110 infusion and LD chemotherapy dose regimen will be further evaluated for efficacy and safety in the Phase 2 part of the study. See Section 4.2.1 for LD regimen and CTX110 infusion plan.

5. STUDY TREATMENT

5.1. Daratumumab Administration in Phase 1

Subjects in Cohort C will receive 1 dose of daratumumab 16 mg/kg by IV infusion or 1800 mg by subcutaneous (SC) injection administered at least 1 day prior to starting LD chemotherapy and within 10 days of CTX110 infusion (see Table 3). For NHL subjects in Cohort C1 who respond to treatment (i.e., achieve SD or better on Day 28), 2 additional doses of daratumumab (16 mg/kg) will be administered at the Day 28 (± 4 days) and M2 (± 4 days) visits. For subjects in Cohort C2 who respond to treatment (i.e., achieve SD or better on Day 28), an additional dose of daratumumab will be administered at the Day 28 visit and an additional infusion of CTX110 will be administered on Day 35. A second additional daratumumab dose will be administered as part of the LD regimen for Day 35 unless within 14 days of the previous Day 28 dose.

The first dose of daratumumab will be delayed if any of the criteria for delayed lymphodepletion as described in Section 5.2 are present.

To be considered for any additional doses of daratumumab, subjects must meet the following criteria at the time of daratumumab dosing:

- No severe or unmanageable toxicity with prior daratumumab doses
- No ongoing uncontrolled infection
- Platelet count ≥25,000 cells/µL (nontransfused)

Daratumumab administration (including pre- and postdose medications, preparation, infusion rates when administered by IV infusion, postdose monitoring) will be performed according to the approved prescribing information. To facilitate administration, the first 16 mg/kg IV dose may be split (to 8 mg/kg) over 2 consecutive days.

After at least 3 subjects are treated at a specific CTX110 dose with daratumumab, the sponsor along with the SRC will review the total safety and efficacy data and may decide to enroll additional subjects at a specific dose level with a lower dose of daratumumab (8 mg/kg IV). Confirmation of tumor response will be based on the PET/computed tomography (CT) scan at the Day 28 visit, and the scan must be read before repeat dosing with daratumumab.

5.1.1. Daratumumab Infusion Reactions

To reduce the risk of infusion reactions with daratumumab, 1 to 3 hours prior to administration subjects will be premedicated with corticosteroids (e.g., IV methylprednisolone 100 mg or equivalent), antipyretics (e.g., oral acetaminophen [paracetamol] 650 to 1,000 mg, or equivalent), and antihistamines (e.g., oral or IV diphenhydramine hydrochloride [or another H1-antihistamine] 25 to 50 mg, or equivalent).

If alternative premedication methods are preferred, the site needs to discuss these with and gain approval from the medical monitor.

Subjects will be monitored frequently during the entire administration of each dose of daratumumab. For infusion reactions of any grade/severity, infusion will be interrupted immediately, and symptoms managed. If an anaphylactic reaction or life-threatening (grade 4) reaction occurs, therapy will be permanently discontinued, and appropriate emergency care will

be administered. For subjects with grade 1, 2, or 3 reactions, after symptom resolution, the infusion rate will be reduced when restarting the infusion as described in approved prescribing information or per site practice.

To reduce the risk of delayed infusion reactions, oral corticosteroids (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) will be administered to subjects following infusion as per prescribing information.

For the second or third dose of daratumumab, intermediate-acting corticosteroids (i.e., prednisone, methylprednisone) should be preferentially used to reduce the risk of interference with CTX110.

If a subject has an unresolved infusion reaction after daratumumab treatment, LD chemotherapy should be delayed and discussed with the medical monitor prior to proceeding.

5.1.2. Additional Considerations

Daratumumab has been associated with herpes zoster (2%) and hepatitis B (1%) reactivation in patients with multiple myeloma. To prevent herpes zoster reactivation, initiate antiviral prophylaxis within 1 week after infusion and continue for 3 months following treatment. For subjects with latent hepatitis B, consider hepatitis B prophylaxis prior to initiation of daratumumab and for 3 months following treatment (King et al., 2018).

Supportive care should be provided according to the approved prescribing information.

Daratumumab binds to CD38 on red blood cells and results in a positive indirect antiglobulin test (indirect Coombs test). Blood type and screen per the approved prescribing information to prevent interference with blood compatibility testing.

5.1.3. Daratumumab Dose Rationale

Daratumumab is a human immunoglobulin G1 monoclonal antibody that targets CD38 surface antigen. CD38 is overexpressed in hematologic malignancies, including multiple myeloma, and daratumumab is thought to exert anticancer efficacy through several mechanisms, including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis via cross-linking. CD38 is also expressed on various immune cell populations, including regulatory and activated T cells, B cells, myeloid-derived suppressor cells, and NK cells, and daratumumab has several demonstrated immunoregulatory modes of actions (Casneuf et al., 2017; Castella et al., 2019; Krejcik et al., 2016).

The goal of daratumumab administration in this study is to utilize these immunomodulatory effects to induce an immune environment amenable to allogeneic CAR T cells. [redacted] The use of a monoclonal antibody (median [± standard deviation] half-life of 18 ± 9 days) is intended to deepen and prolong the immunosuppressive effects achieved with LD chemotherapy alone. Analogous strategies of combining a biologic (e.g., alemtuzumab, an anti-CD52 monoclonal antibody) with chemotherapy-based lymphodepletion have been successfully pursued in other allogeneic CAR T studies (Benjamin et al., 2020). However, given the broad expression of CD52 across the immune system and the known significant

immunosuppression associated with alemtuzumab, [redacted] As mentioned in Section 1.6, CTX110 is an allogeneic CAR T cell with disruption of the B2M locus, resulting in elimination of MHC class I expression on the cell surface, NK cells can potentially detect and clear these "nonself" MHC class I negative cells (Paul and Lal, 2017). [redacted]

Daratumumab was previously evaluated for safety and efficacy in a Phase 2, proof-of-concept trial in subjects with relapsed/refractory NHL, including DLBCL, FL, and mantle cell lymphoma (MCL; N = 138). Daratumumab (16 mg/kg; 28-day cycles) was administered IV weekly for

2 cycles, every 2 weeks for 4 cycles, and every 4 weeks thereafter. Median CD38 expression across treated subjects was 70%. The ORR was 6.7%, 12.5%, and not evaluable in the DLBCL, FL, and MCL cohorts, respectively. The most common grade 3 or 4 treatment-emergent adverse event (TEAE) was thrombocytopenia (11.1%), and 4 (11.1%) subjects discontinued treatment because of TEAEs. Infusion-related reactions occurred in 72.2% of subjects, and the most common reaction was cough (DLBCL cohort: 26.7%; FL cohort: 25.0%; MCL cohort: 80.0%). One subject in each cohort reported a grade 3 infusion-related reaction on Cycle 1, Day 1, which included 2 cases of hypertension, 1 case of pharyngeal edema, and 1 swollen tongue. No grade 4 infusion-related reactions were reported. All infusion-related reactions occurred during the first infusion and recovered/resolved on the same onset date. In conclusion, although this study failed to demonstrate clinically meaningful activity of single-agent daratumumab in the NHL patient population, it did confirm that there were no safety concerns with use of daratumumab in subjects with NHL. All subjects with evaluable samples were found to be negative for [redacted] and the PK of daratumumab were found to be consistent with the results observed in multiple myeloma studies (Salles et al., 2019).

The proposed daratumumab dosage (16 mg/kg IV) used in this protocol is consistent with the doses investigated in the 2 registrational clinical trials in subjects with relapsed or refractory multiple myeloma (Lokhorst et al., 2015; Lonial et al., 2016) and in the proof-of-concept trial in subjects with relapsed or refractory NHL subtypes (Salles et al., 2019). Daratumumab is also available as an SC injection of 1800 mg that is co-formulated with 30,000 units of hyaluronidase-fihj, which increases permeability of the SC tissue by depolymerizing hyaluronan. The daratumumab and hyaluronidase-fihj SC formulation has been shown to be noninferior to the IV formulation and is approved for the treatment of patients with multiple myeloma. In summary, the IV and SC formulations were shown to be comparable in terms of efficacy and PK, with fewer infusion reactions based on a noninferiority trial in multiple myeloma (Mateos et al., 2020). Daratumumab administered SC was noninferior to daratumumab 16 mg/kg administered IV, as measured by ORR (41% vs 37%, respectively) and maximum C_{trough} (593 ± 306 µg/mL vs 522 ± 226 µg/mL, respectively; geometric mean ratio of 108%). The incidence of administration-related reactions was significantly lower with SC daratumumab (13%) compared with IV daratumumab (34%) (Mateos et al., 2020).

5.2. Lymphodepleting Chemotherapy

Phase 1

All subjects in all cohorts will receive LD chemotherapy prior to infusion of first CTX110 infusion and before additional infusions, as specified in Section 5.3.1.

Prior to first CTX110 infusion for Cohorts A, C, and D, and prior to additional CTX110 infusions for all cohorts, LD chemotherapy will consist of:

- Fludarabine 30 mg/m^2 IV daily for 3 doses **AND**
- Cyclophosphamide 500 mg/m^2 IV daily for 3 doses.

For Cohort B, LD chemotherapy prior to first CTX110 infusion will consist of:

- Fludarabine 30 mg/m^2 IV daily for 3 doses **AND**
- Cyclophosphamide 750 mg/m^2 IV daily for 3 doses.

Phase 2

Prior to first CTX110 infusion and prior to additional CTX110 infusions, LD chemotherapy will consist of:

- Fludarabine 30 mg/m^2 IV daily for 3 doses **AND**
- Cyclophosphamide 500 mg/m^2 IV daily for 3 doses.

Phase 1 and Phase 2

Both LD agents (fludarabine and cyclophosphamide) will be started on the same day and administered for 3 consecutive days. Subjects should start LD chemotherapy (or daratumumab administration) within 7 days of study enrollment. Adult subjects with moderate impairment of renal function (creatinine clearance 30-70 mL/min/1.73 m^2) may receive a reduced dose of fludarabine in accordance with applicable prescribing information.

Reference the current full prescribing information for fludarabine and cyclophosphamide for guidance regarding the storage, preparation, administration, supportive care instructions, and toxicity management associated with LD chemotherapy.

For subjects in all cohorts, LD chemotherapy or first daratumumab dose (subjects in Phase 1 Cohort C) will be delayed if any of the following signs or symptoms are present:

- Significant worsening of clinical status that, according to the investigator, increases the potential risk of AEs associated with LD chemotherapy
- Requirement for supplemental oxygen to maintain a saturation level >91%
- New uncontrolled cardiac arrhythmia
- Hypotension requiring vasopressor support
- Active infection: Positive blood cultures for bacteria, fungus, or virus not responding to treatment, or negative culture but active infection based on investigator judgment in consultation with the medical monitor
- Grade ≥2 acute neurological toxicity
- Unresolved infusion reaction due to daratumumab treatment (Phase 1 Cohort C only)

See Section 5.3.1.3 and Section 5.3.1.3.1 for additional criteria that may affect administration of LD chemotherapy.

During Phase 1, Part A (dose escalation), if LD chemotherapy is delayed more than 30 days or the subject starts [redacted] the subject will be replaced. For subjects whose toxicity(ies) are driven by underlying disease and require [redacted] they must subsequently meet disease inclusion criteria, treatment washout, and end organ function criteria before restarting LD chemotherapy. Additionally, any subject who received [redacted] after enrollment (besides LD chemotherapy for all cohorts or daratumumab for Cohort C) must have disease evaluation (including PET/CT scan) performed prior to starting LD chemotherapy (Cohorts A, B, and D) or daratumumab (Cohort C).

5.2.1. Lymphodepleting Chemotherapy Dose Rationale

The goal of lymphodepletion is to allow for significant CAR T cell expansion following infusion. LD chemotherapy consisting of fludarabine and cyclophosphamide across different doses has been successfully utilized in several autologous CAR T cell trials. The rationale for the use of LD chemotherapy is to eliminate regulatory T cells and other competing elements of the immune system that act as [redacted] enhancing the availability of [redacted] such as [redacted] (Dummer et al., 2002; Gattinoni et al., 2005). Additionally, it is postulated that naïve T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naïve T cells are reduced below a certain threshold (Dummer et al., 2002). Cohorts A, C, and D will use cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) at doses that are consistent with doses used in registrational clinical trials of axicabtagene ciloleucel. Cohort B will use a higher dose of cyclophosphamide (750 mg/m^2) prior to first CTX110 infusion to evaluate whether increased intensity of lymphodepletion may facilitate expansion of an allogeneic CAR T cell product in subjects who received prior treatment with an approved autologous CD19-directed CAR T cell therapy. Doses of cyclophosphamide within this range (total of >120 mg/kg or 3 g/m^2) have been used in prior CAR T cell therapy studies in hematological malignancies (Brentjens et al., 2011; Kochenderfer et al., 2015; Turtle et al., 2016). When used as a part of higher intensity LD chemotherapy, increased doses of cyclophosphamide are associated with improved efficacy (Hirayama et al., 2019). In preliminary results from a study of the allogeneic CAR T cell therapy PBCAR0191 in relapsed autologous CAR T cell therapy subjects, an LD regimen of 30 mg/m^2 fludarabine for 4 days + 750 mg/m^2 cyclophosphamide for 3 days (similar to the LD regimen for Cohort B) showed peak expansion of PBCAR0191 and resulted in 100% ORR (11/11 subjects) and 73% CR (8/11 subjects) (Precision Biosciences, 2022).

5.3. Administration of CTX110

CTX110 consists of allogeneic T cells modified with CRISPR-Cas9, [redacted] A flat dose of CTX110 (based on CAR T cells) will be administered as a single IV infusion. A dose limit of [redacted] TCR$^+$ cells/kg will be imposed for all dose levels. [redacted] Infusion should preferably occur through a central venous catheter. A leukocyte filter must not be used.

Prior to the start of CTX110 infusion, the site pharmacy must ensure that 2 doses of tocilizumab and emergency equipment are available for each specific subject treated. Subjects should be premedicated per the site standard of practice with acetaminophen PO (i.e., paracetamol or its equivalent per site formulary) and diphenhydramine hydrochloride IV or PO (or another H1-antihistamine per site formulary) approximately 30 to 60 minutes prior to CTX110 infusion. **Prophylactic systemic corticosteroids should not be administered, as they may interfere with the activity of CTX110.**

Refer to Section 5.4.2 for a list of medications that must be discontinued prior to CTX110 infusion.

Each CTX110 infusion will be delayed if any of the following signs or symptoms are present:

- New active uncontrolled infection

- Worsening of clinical status compared to prior to start of LD chemotherapy that, in the opinion of the investigator, places the subject at increased risk of toxicity
- Grade ≥2 acute neurological toxicity

Each CTX110 infusion will be administered at least 48 hours (but no more than 7 days) after the completion of LD chemotherapy. If CTX110 infusion is delayed by more than 10 days, LD chemotherapy must be repeated. Contact the CRISPR medical monitor if a subject's CTX110 infusion is delayed. Refer to Section 5.3.1 for information regarding additional CTX110 infusions.

Refer to the Infusion Manual for detailed instructions on preparation, storage, handling, and administration of CTX110.

5.3.1. Additional CTX110 Infusion(s)

5.3.1.1. Rationale for CTX110 Additional Infusions

Subjects dosed with CTX110 have achieved objective responses without multi-log CAR T cell expansion in peripheral blood, suggesting a different biology and cell behavior than autologous CAR T cells. [redacted] As allogeneic CAR T cells may be susceptible to more rapid clearance than autologous CAR T cells upon lymphocyte recovery, it therefore may be necessary to administer more than a single infusion to clear any remaining cancerous cells. In order to achieve greater responses and prolonged durability, the sponsor is proposing additional CTX110 infusions in subjects who do not experience significant toxicity following the first CTX110 infusion.

Additional infusions of CTX110 are proposed based on the safety profile demonstrated in Study CRSP-ONC-001 as of 10 April 2022, which includes 61 subjects treated at 5 different dose levels (DL1, DL2, DL3, DL3.5, and DL4) in Phase 1 of the study, and which is largely consistent with other CD19-directed CAR T cell therapies. See Section 1.8 and refer to the CTX110 Investigator's Brochure for the preliminary clinical safety data for CTX110.

As of the data cutoff date of 10 April 2022, 18 subjects with NHL had received a second infusion of CTX110 in Phase 1 of the study. Nine of these subjects received the second infusion as part of the dose regimen of the first course of treatment (4 in Part A Cohort A, 1 in Part A Cohort C, and 4 in Part B cohort expansion). The other 9 subjects responded to the initial CTX110 infusion, subsequently had disease progression, and received the second CTX110 infusion as a second course of treatment (all in Part A Cohort A). The incidence and severity of AEs was similar after first and second infusion. In Part A Cohort A (inclusive of legacy Cohort F), AESIs were reported in 14 of 32 subjects (43.8%) after first CTX110 infusion and in 6 of 13 subjects (46.2%) after second CTX110 infusion. CRS was reported in 13 subjects (40.6%) after the first infusion and in 6 subjects (46.2%) after second infusion, all grade 1 or grade 2 per Lee 2019 criteria. After first infusion, ICANS was reported in 3 subjects (9.4%), opportunistic or invasive infections in 3 subjects (9.4%), and hypogammaglobulinemia in 1 subject (3.1%). After second infusion, opportunistic or invasive infection was reported in 1 subject (7.1%) and there were no

reports of ICANS or hypogammaglobulinemia. The sponsor considers this an acceptable safety profile to investigate the potential efficacy improvements that may come from a second CTX110 infusion.

Preliminary data from other allogeneic anti-CD19 CAR T cell development programs have also suggested multiple infusions may have a favorable benefit-risk profile. Notably, it was recently reported that a subject with relapsed/refractory DLBCL who responded and subsequently progressed after their first infusion of ALLO-501 achieved a CR upon receiving a second infusion of allogeneic CAR T cells (Neelapu et al., 2020) ClinicalTrials.gov Identifier: NCT03939026). Of 6 subjects who received 2 infusions of ALLO-501A in the ALPHA2 trial, none experienced CRS, ICANS, or GvHD (Allogene Therapeutics, 2021). Recently, data were presented from another subject, with adult B cell ALL, who received a second infusion of PBCAR0191 on Day 10 without LD chemotherapy. The subject tolerated the second infusion and received a third infusion of PBCAR0191 on Day 28 with LD chemotherapy. The subject did not experience ICANS or GvHD. Out of 11 adult ALL subjects treated on that trial, 5 had grade 1 or 2 CRS; however, it is unclear from the available information if any of those subjects received multiple infusions of CAR T cells (Precision Biosciences, 2020).

Taken together, the sponsor believes that the current benefit-risk profile of CTX110 in addition to the available clinical data with CTX110 and other allogeneic CAR T cell therapies collectively support further investigating the safety and efficacy of multiple infusions in order to enhance clinical responses and prolong durability within this patient population.

5.3.1.2. Administration Schedule for Subsequent Infusions of CTX110

This study will allow for up to 3 infusions of CTX110 for each subject.

The additional CTX110 infusions after Day 1 will occur in the following 2 scenarios:

1. In the first course of treatment, additional infusions will be based on disease response criteria. In Phase 1, these additional infusions will be administered in all cohorts except Subcohort C1 (see tabulation below and details in Section 5.3.1.3).

Cohort	Additional CTX110 Infusions after Day 1 Within the First Course of Treatment
A and B	A second infusion of CTX110 on Day 35 (-7 days/+21 days) administered with LD chemotherapy to subjects who achieve SD or better at Day 28 scan (based on Lugano criteria). Note: For LD chemotherapy for Cohort B, cyclophosphamide dose will be 750 mg/m^2 prior to first CTX110 infusion, and 500 mg/m^2 prior to subsequent CTX110 infusion.
C2	A second infusion of CTX110 on Day 35 (-7 days/+21 days) administered with daratumumab and LD chemotherapy to subjects who achieve SD or better at Day 28 scan (based on Lugano criteria).
D1 and D2	A second infusion of CTX110 on Day 35 (-7 days/+21 days) administered with LD chemotherapy if the subject has a decrease in BM blast count at Day 28 of ≥50% or is MRD-positive (Subcohort D1) or has demonstrated a reduction in detectable MRD and remain MRD positive (Subcohort D2).

Note: In all cohorts described above, a subject may receive the Day 35 infusion without the LD regimen if experiencing significant cytopenias.

2. For all Phase 1 cohorts and in Phase 2, a second course of treatment consisting of a single CTX110 infusion with LD chemotherapy may be administered after PD if the subject has demonstrated clinical benefit after the first course of treatment. The additional infusion after PD must be within 18 months of the initial CTX110 infusion and ≥4 weeks from the prior CTX110 infusion (Section 5.3.1.4). Subjects in Cohort D who are [redacted] and become MRD-positive without increase in BM blast count may be considered for a second course of treatment.

To receive an additional CTX110 infusion after Day 1, subjects must meet the criteria and repeat some of the screening assessments specified in Sections 5.3.1.3 and 5.3.1.4. All CTX110 infusions subsequent to Day 1 should be discussed in advance with the medical monitor.

Phase 2 will follow the same additional infusions for the first course of treatment and a second course of treatment as determined for Cohort A expansion in Part B of Phase 1 (see Section 4.2.1 for the Phase 2 dose regimen, including additional CTX110 infusions).

5.3.1.3. Criteria for Day 35 CTX110 Infusions Within the First Course of Treatment

For second infusions of CTX110 in Phase 1 Cohorts A, B, C2, and D and in Phase 2 (Day 35), subjects must meet the following criteria:

- No prior DLT during dose escalation (if applicable)
- No prior grade ≥3 CRS without resolution to grade ≤2 within 72 hours following CTX110 infusion per ASTCT criteria
- No prior GvHD following initial CTX110 infusion
- Grade 1, 2, or 3 ICANS must have resolved more than 14 days prior to a subsequent CTX110 infusion
- No prior grade 4 ICANS

Additionally, at the time of LD chemotherapy and prior to second infusion (Day 35), subjects must meet the following criteria:

- ECOG performance status 0 or 1
- No requirement for supplemental oxygen to maintain a saturation level >91%
- No new uncontrolled cardiac arrhythmia
- No hypotension requiring vasopressor support or fluid bolus
- No active uncontrolled infection (positive blood cultures for bacteria, fungus, or virus not responding to treatment)
- Renal: Estimated glomerular filtration rate >50 mL/min/1.73 m^2
- Liver: AST or ALT <3 × ULN; total bilirubin <1.5 × ULN (for subjects with Gilbert's syndrome, total bilirubin <2 mg/dL)
- No worsening of clinical status compared to prior CTX110 infusion that, in the opinion of the investigator, places the subject at increased risk of toxicity.

- No new neurological symptoms suggesting CNS disease involvement. In the case of a normal finding on lumbar puncture or brain MRI and following resolution of neurologic symptoms, additional CTX110 infusions could be considered.
- Women who are pregnant or breastfeeding are not eligible for additional CTX110 infusions.

Local laboratory testing performed within 14 days of planned start of lymphodepletion may be used to confirm eligibility for subsequent CTX110 infusions. Not all central lab screening samples may be required; refer to Laboratory Manual for details.

In the first course of treatment, prior to second CTX110 infusion, LD chemotherapy may be omitted for subjects with platelet count <25,000 cells/µL or ANC <500/mm^3 (unless alternative etiologies for cytopenias are provided; see Section 5.3.1.3.1 for further details).

Subjects who receive an additional infusion should be followed per the schedule of assessments in Table 16, consistent with their initial infusion, with the following considerations:

- Echocardiogram (unless new cardiac signs or symptoms), brain MRI, and lumbar puncture (unless new neurological symptoms concerning for progression) are not required.
- The requirement to confirm CD19 expression is optional in Subcohort D2.
- PET/CT must be performed within 4 weeks of the additional infusion.
- Bone marrow biopsy and aspirate must be repeated within 28 days of the additional infusion in subjects with NHL and B cell ALL with initial bone marrow involvement.

The investigator may choose not to administer the second CTX110 infusion if there is a concern for increased risk or lack of benefit to the subject based on the subject's current clinical status.

5.3.1.3.1. Cytopenia and LD Chemotherapy

During the first course of treatment, in subjects with significant cytopenias (ANC <500/mm^3 and/or platelets <25,000 cells/µL), the investigator may omit LD chemotherapy prior to the second CTX110 infusion (Day 35). Individual cases may be discussed with medical monitor, if there is strong evidence of cytopenias being due to alternative etiologies or expected recovery (including underlying malignancy especially for subjects with B cell ALL).

The sponsor will continue to evaluate subjects who receive additional infusions with LD chemotherapy for prolonged cytopenias. After at least 6 subjects receive an additional infusion with LD chemotherapy in cohort expansion, if >50% of subjects have prolonged grade 3 or 4 cytopenias (i.e., lasting more than 28 days post infusion), use of LD chemotherapy prior to additional infusions will be reconsidered while the sponsor and the SRC reassess current schema and propose an alternate regimen.

In cohort expansion, in subjects who on Day 28 had SD or better and subsequently receive an additional CTX110 infusion without LD chemotherapy, if 8 subjects are infused and all have progressive disease or there is no improvement in response observed based on imaging 28 days after the last infusion, the option of subsequent infusions without LD chemotherapy will be removed and subsequent subjects will receive additional infusions of CTX110 with LD

chemotherapy or will not receive additional infusions of CTX110. See Section 5.2 for LD chemotherapy details.

5.3.1.4. Second Course of Treatment After Progressive Disease for All Cohorts

For all Phase 1 cohorts and in Phase 2, a subject may receive an additional infusion of CTX110 after PD if the subject has a clinical response after the first course of treatment. Subjects must have achieved evidence of clinical benefit, as demonstrated by a decrease in tumor size and/or FDG-avidity on a PET/CT scan after CTX110 infusion for subjects with NHL and by ≥50% decrease in BM blasts or achieving [redacted] remission for subjects with adult B cell ALL, and either concurrently or subsequently progressed or relapsed. The additional infusion after PD must be within 18 months of the initial CTX110 infusion and ≥4 weeks from the prior CTX110 infusion. The additional CTX110 infusion will be administered only if the extent of disease is less than what was documented prior to the initial CTX110 infusion and will proceed only after consultation with the medical monitor. Subjects with B cell ALL who have become MRD-positive after achieving [redacted] remission may also be considered for a second course of treatment. The second course of treatment will be administered with standard lymphodepletion (i.e., without daratumumab) for subjects in Phase 1 Cohort C.

The earliest time at which a subject could be receive a CTX110 infusion after PD is ≥4 weeks following last CTX110 infusion. The additional infusion in subjects with grade 3 or 4 neutropenia or thrombocytopenia who are ≥4 weeks after last CTX110 infusion will not be permitted unless the cytopenias can be clearly attributed to PD or other reversible cause.

To receive the second course of treatment with an additional CTX110 infusion, subjects must meet the following criteria:

- Confirmation tumor (NHL) or bone marrow (ALL) remains $CD19^+$ at relapse (by flow cytometry or immunohistochemistry); the requirement to confirm CD19 expression is optional in subjects with B cell ALL with only MRD positive disease.
- No prior DLT during dose escalation (if applicable)
- No prior grade ≥3 CRS without resolution to grade ≤2 within 72 hours following CTX110 infusion
- No prior GvHD following CTX110 infusion
- No prior grade ≥2 ICANS following CTX110 infusion
- Meet initial study inclusion criteria (#1, #2, #5 through#9) and exclusion criteria (#1 [except prior treatment with CTX110] through #14), as described in Section 3
- Meet criteria for LD chemotherapy and CTX110 infusion, as described in Sections 5.2 and 5.3, respectively
- Subjects who are reinfused after PD should be followed per the schedule of assessments in Table 16.

All Stage 1 screening assessments (see Schedule of Assessments) must be repeated, including the following additional considerations:

- Brain MRI and lumbar puncture to be repeated if at high risk for CNS recurrence based on International Prognostic Index criteria (Schmitz et al., 2016) or signs of CNS involvement are present at the time of the additional infusion. All subjects with adult B cell ALL must have a repeat of lumbar puncture (LP) prior to additional infusion.
- Echocardiogram may be omitted if the additional infusion occurs within 3 months of last CTX110 infusion when echocardiogram was performed and if no new cardiac symptoms have occurred.
- For NHL cohorts: The PET/CT scan demonstrating disease relapse/progression will serve as the new baseline for tumor response evaluation. The additional infusion must occur within 28 days of that scan. Bone marrow aspirate and biopsy must be repeated if it was not performed at the time of relapse/progression.
- For adult B cell ALL cohorts: Bone marrow aspirate and biopsy (as well as imaging for subjects with extramedullary disease) within 28 days of LD chemotherapy.

Subjects who receive an additional CTX110 infusion after PD will receive a lymphodepletion regimen according to their initial cohort design and a CTX110 dose that at the time of the additional infusion has been deemed safe by the SRC. Exception will be made for subjects in Cohort B or C, who may receive lymphodepletion similar to Cohort A after discussion with medical monitor.

In subjects who have more than 1 infusion prior to disease progression, disease response assessments will continue using the baseline PET/CT scan and bone marrow biopsy performed during screening. For subjects who receive an additional CTX110 infusion after PD, disease response will be assessed relative to the most recent PET/CT scan and bone marrow prior to the additional infusion.

5.3.2. CTX110 Postinfusion Monitoring

Following CTX110 infusion, subject's vitals should be monitored every 30 minutes for 2 hours after infusion or until resolution of any potential clinical symptoms.

Subjects in Phase 1 Part A will be hospitalized for a minimum of 7 days after CTX110 infusion, or longer if required by local regulation or site practice (Appendix D). In Phase 1 Part A (dose escalation, subjects must remain in proximity of the investigative site (i.e., 1-hour time) for at least 28 days after CTX110 infusion. For Phase 1 Part B (cohort expansion) and Phase 2, subjects must remain within proximity of the investigative site (i.e., 1-hour transit time) for 28 days after the first CTX110 infusion and at least 14 days for subsequent CTX110 infusions, or longer if justified by subject's clinical status or as required by local regulation or site practice. Management of acute CTX110-related toxicities should occur **ONLY** at the study site.

Subjects will be monitored for signs of CRS, TLS, neurotoxicity, GvHD, and other AEs according to the schedule of assessments (Table 16, Table 17, and Table 18).

Guidelines for the management of CAR T cell–related toxicities are described in Section 6. Subjects should remain hospitalized until CTX110-related nonhematologic toxicities (e.g., fever, hypotension, hypoxia, ongoing neurological toxicity) return to grade 1. Subjects may remain hospitalized for longer periods if considered necessary by the treating investigator.

5.3.3. Investigational Product Accountability

The investigator and sponsor are responsible for accountability and traceability of CTX110 clinical supply.

The investigator will ensure that CTX110 is used in accordance with this protocol. Detailed accountability records indicating CTX110 inventory at each clinical site, use by each subject, and disposal will be maintained by the clinical sites. These records will document which subjects were provided the CTX110 dose as specified in the protocol and will reconcile CTX110 received by the subject. To maintain compliance, the sponsor or its designee will review CTX110 clinical supply accountability records at the clinical sites on an ongoing basis during monitoring visits.

All excess material containing CTX110 will be considered hazardous waste and disposed of in compliance with applicable regulations and standard hospital procedures. Destruction will be adequately documented and reviewed regularly by the sponsor or its designee and the investigator.

In cases in which daratumumab is supplied by the sponsor, the investigator and sponsor are responsible for accountability and traceability of daratumumab clinical supply in a manner similar to that for CTX110, as described above.

5.4. Prior and Concomitant Medications

5.4.1. Allowed Medications

Necessary supportive measures for optimal medical care will be given throughout the study, including IV antibiotics to treat infections, growth factors, blood components, etc., except for prohibited medications listed in Section 5.4.2.

All concurrent therapies, including prescription and nonprescription medication, must be recorded from the date of signed informed consent through 3 months after CTX110 infusion. Beginning 3 months post-CTX110 infusion, only the following selected concomitant medications will be collected: IV immunoglobulins, vaccinations, [redacted] immunosuppressants (including steroids), and any investigational agents.

5.4.2. Prohibited Medications

The following medications are prohibited during certain periods of the study as specified below:

- Corticosteroid therapy at a pharmacologic dose (>10 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs should be avoided after CTX110 administration unless medically indicated to treat new toxicity or as part of management of CRS or neurotoxicity associated with CTX110, as described in Section 6. Use of oral corticosteroids before and after daratumumab administration is permitted to prevent infusion reactions, as described in Section 5.1.
- Granulocyte-macrophage colony-stimulating factor (GM-CSF) following CTX110 infusion due to the potential to worsen symptoms of CRS
- Granulocyte colony-stimulating factor (G-CSF) is prohibited following CTX110 infusion but may be administered ≥10 days following CTX110 infusion if subject

shows no signs of CRS. In addition, for cohorts that receive 2 CTX110 infusions with LD chemotherapy in a regimen, proactive use of G-CSF starting ≥10 days following the first CTX110 infusion is recommended to support the second round of LD chemotherapy.

- Intrathecal CNS prophylaxis must be stopped at least 7 days prior to CTX110 infusion.

[redacted]

6. TOXICITY MANAGEMENT

6.1. General Guidance

Subjects must be closely monitored for at least 28 days after CTX110 infusion. Significant toxicities have been reported with autologous CAR T cell therapies and investigators are required to **proactively monitor and treat all adverse events in accordance with protocol guidance**.

Although this is a first-in-human study and the clinical safety profile of CTX110 has not been described, the following general recommendations are provided based on prior experience with CD19-directed autologous CAR T cell therapies:

- Fever is the most common early manifestation of CRS; however, subjects may also experience weakness, hypotension, or confusion as first presentation.
- Diagnosis of CRS should be based on clinical symptoms and **NOT** laboratory values.
- In subjects who do not respond to CRS-specific management, always consider sepsis and resistant infections. Subjects should be continually evaluated for resistant or emergent bacterial infections, as well as fungal or viral infections.
- CRS, HLH, and TLS may occur at the same time following CAR T cell infusion. Subjects should be consistently monitored for signs and symptoms of all the conditions and managed appropriately.
- Neurotoxicity may occur at the time of CRS, during CRS resolution, or following resolution of CRS. Grading and management of neurotoxicity will be performed separately from CRS.
- Tocilizumab must be administered within 2 hours from the time of order.

The safety profile of CTX110 will be continually assessed throughout the study, and investigators will be updated on a regular basis with new information regarding the identification and management of potential CTX110-related toxicity (refer to the CTX110 Investigator's Brochure).

6.2. Toxicity-Specific Guidance

6.2.1. Infusion Reactions

Infusion reactions have been reported in autologous CD19-directed CAR T cell trials, including transient fever, chills, and/or nausea. Acetaminophen (paracetamol) and diphenhydramine hydrochloride (or another H1-antihistamine) may be repeated every 6 hours after CTX110 infusion, as needed, if an infusion reaction occurs.

Nonsteroidal anti-inflammatory medications may be prescribed, as needed, if the subject continues to have fever not relieved by acetaminophen. Systemic steroids should not be administered except in cases of life-threatening emergency, as this intervention may have a deleterious effect on CAR T cells.

6.2.2. Febrile Reaction and Infection Prophylaxis

Infection prophylaxis should occur according to the institutional standard of care.

In the event of febrile reaction, an evaluation for infection should be initiated and the subject managed appropriately with antibiotics, fluids, and other supportive care as medically indicated and determined by the treating physician. Viral and fungal infections should be considered throughout a subject's medical management if fever persists. If a subject develops sepsis or systemic bacteremia following CTX110 infusion, appropriate cultures and medical management should be initiated. Additionally, consideration of CRS should be given in any instances of fever following CTX110 infusion within 30 days post infusion.

For Phase 1 Cohort C, prophylaxis for herpes zoster and hepatitis B reactivation in the setting of daratumumab treatment is strongly recommended, as per prescribing information.

For subjects receiving multiple CTX110 infusions with LD chemotherapy, pneumocystis jirovecii prophylaxis is recommended per local guidelines.

6.2.3. Tumor Lysis Syndrome

Subjects receiving CAR T cell therapy are at increased risk of TLS. Subjects should be closely monitored for TLS via laboratory assessments and symptoms from the start of LD chemotherapy until 28 days following CTX110 infusion.

All subjects at risk for TLS should receive prophylactic allopurinol (or a nonallopurinol alternative, such as febuxostat, per institutional guidelines) and increased oral/IV hydration during screening and before initiation of LD chemotherapy. Prophylaxis can be stopped after 28 days following CTX110 infusion or once the risk of TLS passes.

Sites should monitor and treat TLS as per their institutional standard of care, or according to published guidelines (Cairo and Bishop, 2004). TLS management, including administration of rasburicase, should be instituted promptly when clinically indicated.

6.2.4. Cytokine Release Syndrome

CRS is a major toxicity reported with autologous CD19-directed CAR T cell therapy. CRS is due to hyperactivation of the immune system in response to CAR engagement of the target antigen, resulting in multi-cytokine elevation from rapid T cell stimulation and proliferation (Frey et al.,

2014; Maude et al., 2014a). When cytokines are released, a variety of clinical signs and symptoms associated with CRS may occur, including cardiac, gastrointestinal (GI), neurological, respiratory (dyspnea, hypoxia), skin, cardiovascular (hypotension, tachycardia), and constitutional (fever, rigors, sweating, anorexia, headaches, malaise, fatigue, arthralgia, nausea, and vomiting) symptoms, and laboratory (coagulation, renal, and hepatic) abnormalities.

The goal of CRS management is to prevent life-threatening sequelae while preserving the potential for the antitumor effects of CTX110. Symptoms usually occur 1 to 14 days after autologous CAR T cell therapy, but the timing of symptom onset has not been fully defined for allogeneic CAR T cells.

CRS should be identified and treated based on clinical presentation and **not** laboratory cytokine measurements. If CRS is suspected, grading should be applied according to the ASTCT (formerly known as American Society for Blood and Marrow Transplantation) consensus recommendations (Lee et al., 2019) (Table 7), and management should be performed according to the recommendations in Table 8.

At the time of the original protocol version (V1.0), the well-known Lee 2014 CRS grading criteria (Lee et al., 2014) were applied to Part A. However, this has been updated to the ASTCT criteria (Lee et al., 2019), which have become the worldwide standard for CRS grading. Starting with Protocol Version 6.0 (Amendment 5), only the ASTCT criteria will be used during both Parts A and Part B (cohort expansion) of the trial. CRS events previously graded using the Lee criteria (Lee et al., 2014) will be re-graded according to the ASTCT criteria for the purposes of aggregate safety reporting.

Neurotoxicity will be graded and managed as described in Section 6.2.5.

Table 7: Grading of CRS According to ASTCT Consensus Criteria

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[1]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or Hypoxia[2]	None	Requiring low-flow nasal cannula[3] or blow-by	Requiring high-flow nasal cannula[3], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; C: Celsius; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events.
Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
[1.] Fever is defined as temperature ≥38°C not attributable to any other cause. In subjects who have CRS then receive antipyretics or [redacted] such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[2.] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[3.] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Table 8: CRS Management Guidance

CRS Severity[1]	Tocilizumab	Corticosteroids
Grade 1	Tocilizumab[2] may be considered per investigator's discretion in consultation with the medical monitor	N/A
Grade 2	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) [2] Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to ≤3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement within 24 hours after starting tocilizumab, administer methylprednisolone 1 mg/kg IV twice daily. Continue corticosteroid use until the event is grade ≤1, then taper over 3 days.
Grade 3	Per grade 2	Per grade 2
Grade 4	Per grade 2 If no response to multiple doses of tocilizumab and steroids, consider using other [redacted] (e.g., siltuximab, anakinra).	Per grade 2

CRS: cytokine release syndrome; IV: intravenously; N/A: not applicable.
[1.] See Lee et al., 2019.
[2.] Refer to tocilizumab prescribing information.

Throughout the duration of CRS, subjects should be provided with supportive care consisting of antipyretics, IV fluids, and oxygen. Subjects who experience grade ≥2 CRS (e.g., hypotension, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For subjects experiencing grade 3 CRS, consider performing an echocardiogram to assess cardiac function. For grade 3 or 4 CRS, consider intensive care supportive therapy. Intubation for airway protection due to neurotoxicity (e.g., seizure) and not due to hypoxia should not be captured as grade 4 CRS. Similarly, prolonged intubation due to neurotoxicity without other signs of CRS (e.g., hypoxia) is not considered grade 4 CRS. Investigators should always consider the potential of an underlying infection in cases of severe CRS, as the presentation (fever, hypotension, hypoxia) is similar. Resolution of CRS is defined as resolution of fever (temperature ≥38 °C), hypoxia, and hypotension (Lee et al., 2019).

6.2.5. Neurotoxicity

Neurotoxicity has been observed with autologous CD19-directed CAR T cell therapies. Signs and symptoms can be progressive and may include headache, aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. Neurotoxicity may occur at the time of CRS, during the resolution of CRS, or following resolution of CRS, and its pathophysiology is unclear. The ASTCT consensus further defined neurotoxicity associated with CRS as ICANS, a disorder characterized by a pathologic process involving the CNS following any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells (Lee et al., 2019). Potential etiologies of neurotoxicity include ICANS or viral infection. Guidance for differential diagnosis and management follows (see Section 6.2.5.1 for ICANS and Section 6.2.5.2 for viral encephalitis).

Evaluation of any new onset neurotoxicity should include a neurological examination, including ICE assessment tool (Table 10), brain MRI, and examination of the CSF (via LP), as clinically indicated. If a brain MRI is not possible, all subjects should receive a noncontrast CT to rule out intracerebral hemorrhage. LP is required for any grade ≥3 neurotoxicity and is strongly recommended for grade 1 and grade 2 events, if clinically feasible. LP must be performed within 48 hours of symptom onset, unless not clinically feasible. Electroencephalogram should also be considered as clinically indicated. Endotracheal intubation may be needed for airway protection in severe cases.

Nonsedating, antiseizure prophylaxis (e.g., levetiracetam) should be considered in all subjects for at least 21 days following CTX110 infusion or upon resolution of neurological symptoms (unless the investigator considers the antiseizure medication to be contributing to the detrimental symptoms). For severe or life-threatening neurologic toxicities, intensive care supportive therapy should be provided. Neurology consultation should always be considered. Monitor platelets and for signs of coagulopathy and transfuse blood products appropriately to diminish risk of intracerebral hemorrhage. For subjects who receive active steroid management for more than 3 days, antifungal and antiviral prophylaxis is recommended to mitigate a risk of severe infection with prolonged steroid use. Consideration for antimicrobial prophylaxis should also be given (see Section 6.2.2).

In cases of suspected ICANS, subjects should be graded according to the ICANS grading table (Table 9) which incorporates assessment of level of consciousness, presence/absence of seizures, motor findings, presence/absence of cerebral edema, and overall assessment of neurologic domains by using a modified assessment tool called the ICE (immune effector cell–associated encephalopathy) assessment tool (Table 10).

Headache, which may occur in a setting of fever or after chemotherapy, is very common but is a nonspecific symptom. Headache alone may not necessarily be a manifestation of ICANS and further evaluation should be performed. Weakness or balance problem resulting from deconditioning and muscle loss are excluded from definition of ICANS. Similarly, intracranial hemorrhage with or without associated edema may occur due to coagulopathies in these subjects and are also excluded from definition of ICANS. These and other neurotoxicities should be captured in accordance with CTCAE v5.0.

6.2.5.1. ICANS

If ICANS is diagnosed, management should be performed according to Table 11 depending on the ICANS grade (Table 9) and whether the subject has concurrent CRS or not. In addition, nonsteroidal agents (e.g., anakinra, etc.) may be considered for ICANS management after discussion with the CRISPR medical monitor (Neill et al., 2020). Subjects who experience ICANS grade ≥2 should be monitored with continuous cardiac telemetry and pulse oximetry.

Table 9: ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[1]	7-9	3-6	0-2	0 (subject is unarousable and unable to undergo ICE assessment)
Depressed level of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arise; stupor or coma
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[3]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging 4	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

CTCAE: Common Terminology Criteria for Adverse Events; EEG: electroencephalogram; ICANS: immune effector cell–associated neurotoxicity syndrome; ICE: immune effector cell–associated encephalopathy (assessment tool); ICP: intracranial pressure; N/A: not applicable.
ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.
1. A subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
2. Depressed level of consciousness should be attributable to no other cause (e.g., sedating medication).
3. Tremors and myoclonus associated with immune effector therapies should be graded according to CTCAE v5.0 but do not influence ICANS grading.

Table 10: ICE Assessment

Domain	Assessment	Maximum Score
Orientation	Orientation to year, month, city, hospital	4 points
Naming	Name 3 objects (e.g., point to clock, pen, button)	3 points
Following command	Ability to follow commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing	Ability to write a standard sentence (includes a noun and verb)	1 point
Attention	Ability to count backward from 100 by 10	1 point

ICE score will be reported as the total number of points (0-10) across all assessments.
See Section 7.2.12.

Table 11: ICANS Management Guidance

Severity	Management
Grade 1	If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for up to 3 days in consultation with the medical monitor
Grade 2	Consider administering dexamethasone 10 mg IV every 6 hours (or equivalent methylprednisolone) unless subject already on equivalent dose of steroids for CRS. Continue dexamethasone use until event is grade ≤1, then taper over 3 days. Cohorts D and G (B cell ALL only): Strongly consider administration of dexamethasone 10 mg IV every 6 hours.
Grade 3	Administer dexamethasone 10 mg IV every 6 hours, unless subject already on equivalent dose of steroids for CRS. Continue dexamethasone use until event is grade ≤1, then taper over 3 days.
Grade 4	Administer methylprednisolone 1000 mg IV per day for 3 days; if improves, manage as above.

CRS: cytokine release syndrome; ICANS: immune effector cell–associated neurotoxicity syndrome; IV: intravenously.

6.2.5.2. Viral Encephalitis

Reactivation of chronic latent infections has been reported in patients who are highly immunosuppressed, including those who have undergone hematopoietic stem cell transplantation (HSCT) or CAR T cell therapy (Handley et al., 2021; Rebechi et al., 2021). Specifically, there have been 8 reported cases of human herpesvirus 6 (HHV-6) encephalitis following CAR T cell infusion (Spanjaart et al., 2022).

Viral encephalitis can be distinguished from ICANS based on the characteristics described in Table 12. In addition, encephalitis should be considered in subjects who initially respond to ICANS treatment, but subsequently worsen.

Table 12: Differentiating Between ICANS and HHV-6 Encephalitis After CAR T Cell Therapy

	Neurotoxicity After CAR T Cell Therapy (ICANS)	HHV-6 Encephalitis
Clinical presentation	Tremor, dysphagia, expressive aphasia, impaired attention, apraxia, and lethargy	Headache, confusion, or delirium; progresses to anterograde then retrograde amnesia
Timing	Very early (usually within first 3 to 10 days)	Typically within the first 21 days
Progression	Rapidly over hours to days	More slowly, over several days
Associated symptoms	Cytokine release syndrome	Fever is uncommon
Seizures	Less common	Very common
CSF findings	Often normal, may have mildly elevated protein	Mildly abnormal (minimal pleocytosis, slightly elevated protein, normal glucose)
CSF HHV-6	PCR negative	PCR positive
EEG abnormalities	Diffuse slowing	Epileptiform activity
Imaging findings (MRI)	Usually normal, although vasogenic edema, leptomeningeal enhancement, and microhemorrhages	T2/FLAIR/DWI hyperintensities in the medial temporal lobes, especially the amygdala and the hippocampus
Treatment	Corticosteroids and/or [redacted]	Antivirals (ganciclovir, foscarnet, cidofovir)
Outcomes	Highly variable, ranges from complete recovery to significant residual disability and death	Highly variable, ranges from complete recovery to disability and death; majority recover

CAR: chimeric antigen receptor; CSF: cerebrospinal fluid; EEG: electroencephalogram; HHV-6, human herpesvirus 6; [redacted] MRI: magnetic resonance imaging; PCR: polymerase chain reaction; T2/FLAIR/DWI: T2-weighted fluid attenuated inversion recovery/diffusion-weighted imaging.
Source: Adapted from (Rebechi et al., 2021).

In cases of suspected viral encephalitis, the following diagnostic tests are required:

- brain MRI,
- blood (plasma preferred) for HHV-6 DNA PCR, and
- LP for:
  - HHV-6 DNA PCR (should be performed within 48 hours of symptoms if clinically feasible),
  - the standard panel performed at site (which should include at least cell count, Gram stain, and *Neisseria meningitidis*), and
  - CSF PCR analysis for herpes simplex virus (HSV) -1 and -2, enterovirus, varicella zoster virus (VZV), cytomegalovirus (CMV), and HHV-6.

Baseline serology samples will be collected and sent to a central lab and may be tested in the event of viral infection to distinguish between primary infection and reactivation.

Results from the infectious disease panel should be available within 5 business days of the LP in order to appropriately manage the subject. If a site is unable to perform the panel tests, it must be discussed with the medical monitor. For any suspected case of viral encephalitis, the CRISPR medical monitor must be contacted within 24 hours.

HHV-6 management should include the following:

- Primary therapy should include foscarnet and ganciclovir, and second-line therapy should include cidofovir.
- Recommended duration of therapy is 3 weeks. Treatment duration can be increased to 6 weeks in the event of persistent clinical manifestations or ongoing detectable HHV-6 copies in the CSF or peripheral blood.
- An infectious disease consultation is recommended.

6.2.6. B Cell Aplasia

B cell aplasia may occur and will be monitored by following IgG blood levels. IV gammaglobulin should be administered for clinically significant hypogammaglobulinemia (systemic infections, <400 mg/dL) according to institutional standard of care**.**

6.2.7. Hemophagocytic Lymphohistiocytosis

HLH has been reported after treatment with autologous CD19-directed CAR T cells (Barrett et al., 2014; Maude et al., 2014b; Maude et al., 2015; Porter et al., 2015; Teachey et al., 2013). HLH is a clinical syndrome that is a result of an inflammatory response following infusion of CAR T cells in which cytokine production from activated T cells leads to excessive macrophage activation. Signs and symptoms of HLH may include fevers, cytopenias, hepatosplenomegaly, hepatic dysfunction with hyperbilirubinemia, coagulopathy with significantly decreased fibrinogen, and marked elevations in ferritin and C-reactive protein (CRP). Neurologic findings have also been observed (Jordan et al., 2011; La Rosée, 2015).

CRS and HLH may possess similar clinical syndromes with overlapping clinical features and pathophysiology. HLH will likely occur at the time of CRS or as CRS is resolving. HLH is considered an overlap syndrome with CRS and should be treated according to the CRS management guidelines.

The diagnosis of HLH will be confirmed in subjects who meet the criteria in Table 13.

Table 13: Criteria for Diagnosis of HLH

Subjects must meet the following criteria	
Peak serum ferritin level of >10,000 ng/mL during the CRS phase of CAR T cell therapy (typically the first 5 days after cell infusion)	
AND	
Subsequently developed any 2 of the following:	• Grade ≥3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels • Grade ≥3 oliguria or increase in serum creatinine levels • Grade ≥3 pulmonary oedema • Presence of hemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry

CAR: chimeric antigen receptor; CD: cluster of differentiation; CRS: cytokine release syndrome
Adapted from (Neelapu et al., 2018).

HLH may be suspected in the presence of unexplained elevated liver function tests or cytopenias with or without other evidence of CRS. In the event of a suspicion or diagnosis of HLH, the following should be collected:

- serum soluble interleukin-2 receptor (soluble CD25)
- bone marrow biopsy and aspirate may be collected if safe to conduct, for further confirmation. Where feasible, excess bone marrow samples should be sent to a central laboratory. Details of sample preparation and shipment are contained in the Laboratory Manual.

If HLH is suspected or confirmed:

- Frequently monitor coagulation parameters, including fibrinogen. These tests may be done more frequently than indicated in the schedule of assessments, and frequency should be driven based on laboratory findings.
- Fibrinogen should be maintained ≥100 mg/dL to decrease risk of bleeding.
- Coagulopathy should be corrected with blood products.
- Check for soluble CD25 and triglycerides
- If possible, perform bone marrow biopsy to assess for hemophagocytosis.
- Given the overlap with CRS, subjects should also be managed per CRS treatment guidance in Table 8. The [redacted] inhibitor anakinra or other [redacted] may also be considered following discussion with the medical monitor.

Suspected cases of HLH should be discussed with the sponsor's medical monitor.

6.2.8. Cytopenias

Grade 3 neutropenia and thrombocytopenia, at times lasting more than 28 days post infusion, have been reported in subjects treated with autologous CD19-directed CAR T cell products (Kymriah USPI, 2017; Yescarta USPI, 2017). Therefore, subjects receiving CTX110 should be monitored for such toxicities and appropriately supported. Consideration should be given to antimicrobial and antifungal prophylaxis for any subject with prolonged neutropenia. For subjects experiencing grade ≥3 neutropenia, thrombocytopenia, or anemia that has not resolved within 28 days of CTX110 infusion, a complete blood count with differential should be performed more frequently until resolution to grade ≤2 or administration of a new systemic [redacted] They should be performed weekly until 3 months after each CTX110 infusion and then should be performed at least monthly.

G-CSF may be considered in cases of grade 4 neutropenia 10 days post–CTX110 infusion, when the risk of CRS has passed. G-CSF administration may be considered earlier but must first be discussed with the medical monitor. In addition, for cohorts that receive 2 CTX110 infusions with LD chemotherapy in a regimen, proactive use of G-CSF starting ≥10 days following the first CTX110 infusion is recommended to support the second round of LD chemotherapy. Antimicrobial and antifungal prophylaxis should be considered for any subject with prolonged neutropenia or on high doses of steroids.

For Phase 1 Cohort C, daratumumab may increase neutropenia and/or thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to the manufacturer's prescribing information for background therapies. Monitor subjects with neutropenia for signs of infection. Daratumumab dose delay may be required to allow recovery of neutrophils and/or platelets, as per prescribing information. Consider supportive care with growth factors for neutropenia or transfusions for thrombocytopenia.

6.2.9. Graft vs Host Disease

GvHD is seen in the setting of allogeneic HSCT and is the result of immunocompetent donor T cells (the graft) recognizing the recipient (the host) as foreign. The subsequent immune response activates donor T cells to attack the recipient to eliminate foreign antigen–bearing cells. GvHD is divided into acute, chronic, and overlap syndromes based on both the time from allogeneic HSCT and clinical manifestations. Signs of acute GvHD may include a maculopapular rash; hyperbilirubinemia with jaundice due to damage to the small bile ducts, leading to cholestasis; nausea, vomiting, and anorexia; and watery or bloody diarrhea and cramping abdominal pain (Zeiser and Blazar, 2017).

To support the proposed clinical study, a nonclinical Good Laboratory Practice–compliant GvHD and tolerability study was performed in immunocompromised mice at 2 doses that exceed all proposed clinical dose levels by at least 10-fold. Further, due to the specificity of CAR insertion at the TRAC locus, it is highly unlikely for a T cell to be both CAR^+ and TCR^+. Remaining TCR^+ cells are removed during the manufacturing process by immunoaffinity chromatography on an anti-TCR antibody column to achieve ≤0.15% TCR^+ cells in the final product. A limit of [redacted] TCR^+ cells/kg will be imposed for all dose levels. This limit is lower than the limit of 1×10^5 TCR^+ cells/kg based on published reports on the number of allogeneic cells capable of causing severe GvHD during HSCT with haploidentical donors (Bertaina et al., 2014). Through this specific editing, purification, and strict product release criteria, the risk of

GvHD following CTX110 should be low, although the true incidence is unknown. Subjects should be monitored closely for signs of acute GvHD following infusion of CTX110. The timing of potential symptoms is unknown. However, given that CAR T cell expansion is antigen-driven and will likely occur only in TCR^- cells, it is unlikely that the number of TCR^+ cells will appreciably increase above the number infused.

Diagnosis and grading of GvHD should be based on published criteria (Harris et al., 2016), as outlined in Table 14.

Table 14: Criteria for Grading Acute GvHD

Stage	Skin (active erythema only)	Liver (bilirubin mg/dL)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GvHD rash	<2	No or intermittent nausea, vomiting, or anorexia	<500 mL/day or <3 episodes/day
1	Maculopapular rash <25% BSA	2-3	Persistent nausea, vomiting, or anorexia	500-999 mL/day or 3-4 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6	–	1000-1500 mL/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	6.1-15	–	>1500 mL/day or >7 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15	–	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)

BSA: body surface area; GI: gastrointestinal; GvHD: graft vs host disease.

Overall GvHD grade will be determined based on most severe target organ involvement.

- Grade 0: No stage 1-4 of any organ
- Grade 1: Stage 1-2 skin without liver, upper GI, or lower GI involvement
- Grade 2: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
- Grade 3: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI
- Grade 4: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI

Potential confounding factors that may mimic GvHD such as infections and reactions to medications should be ruled out. Skin and/or GI biopsy should be obtained for confirmation before or soon after treatment has been initiated. In instance of liver involvement, liver biopsy should be attempted if clinically feasible. Sample(s) of all biopsies will also be sent to a central laboratory for pathology assessment. Details of sample preparation and shipment are contained in the Laboratory Manual.

Recommendations for management of acute GvHD are outlined in Table 15. To allow for intersubject comparability at the end of the trial, investigators should follow these

recommendations except in specific clinical scenarios in which following them could put the subject at risk.

Table 15: Acute GvHD Management

Grade	Management
1	Skin: Topical steroids or immunosuppressants; if stage 2: methylprednisolone 1 mg/kg (or equivalent dose).
2-4	Initiate methylprednisolone 2 mg/kg daily (or equivalent dose). IV form of steroid such as methylprednisolone should be considered if there are concerns with malabsorption. Steroid taper may begin after improvement is seen after ≥3 days of steroids. Taper should be 50% decrease of total daily steroid dose every 5 days. GI: In addition to steroids, start anti-diarrheal agents per standard practice.

GI: gastrointestinal; IV: intravenous.

Decisions to initiate second-line therapy should be made sooner for subjects with more severe GvHD. For example, secondary therapy may be indicated after 3 days with progressive manifestations of GvHD, after 1 week with persistent grade 3 GvHD, or after 2 weeks with persistent grade 2 GvHD. Second-line systemic therapy may be indicated earlier in subjects who cannot tolerate high-dose glucocorticoid treatment (Martin et al., 2012). Choice of secondary therapy and when to initiate will be based on the treating investigator's clinical judgment and local practice.

Management of refractory acute GvHD or chronic GvHD will be per institutional guidelines. Anti-infective prophylaxis measures should be instituted per local guidelines when treating subjects with immunosuppressive agents (including steroids).

The CRISPR medical monitor should be contacted if a case of GvHD is suspected.

6.2.10. Hypotension and Renal Insufficiency

Hypotension and renal insufficiency have been reported with CAR T cell therapy and should be treated with IV administration of normal saline boluses according to institutional practice guidelines. Dialysis should be considered when appropriate.

6.2.11. Special Consideration During COVID-19 Pandemic

Subjects enrolled in this study undergo LD chemotherapy, are immunocompromised, and at increased risk of infections. Hence, the clinical study protocol requires exclusion of subjects in the case of any ongoing active infection during screening, prior to LD chemotherapy, and prior to CTX110 infusion, or delayed infusions (see Section 3.2).

This measure will include subjects with active infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causal agent of COVID-19 (coronavirus disease-2019). Due to the rapidly changing evidence as well as locoregional differences, the sponsor defers to local regulations and institutional guidelines if the current situation allows a safe conduct of the study for an individual subject at a given time. Whenever possible, a COVID-19 vaccine or booster should not be administered within 4 weeks prior to scheduled imaging for disease assessment. Additionally, the minimal requirements by the sponsor are to be

defined in a memorandum to the study centers that is periodically updated as evidence and guidelines evolve.

7. STUDY PROCEDURES

Both the dose escalation and expansion parts of the study will consist of 3 distinct stages: (1) screening and eligibility confirmation; (2) treatment, consisting of LD chemotherapy (with or without daratumumab) and CTX110 infusion; and (3) follow-up. During the screening stage, subjects are assessed according to the eligibility criteria outlined in Section 3.

After enrollment, subjects in Phase 1 Cohorts A, B, and D and Phase 2 will receive LD chemotherapy followed by infusion of CTX110; subjects in Phase 1 Cohort C will receive daratumumab followed by LD chemotherapy, then CTX110 infusion. Additional CTX110 infusion may be administered with or without respective LD regimen as specified in Table 3 and Section 5.3.1. During follow-up, subjects will be assessed for tumor response, disease progression, and survival. Throughout all study stages, subjects will be regularly monitored for safety.

A complete schedule of assessments is provided in Table 16 for Phase 1 (Parts A and B), Table 17 for Phase 2, and Table 18 for both phases. Descriptions of all required study procedures are provided in this section. In addition to protocol-mandated assessments, subjects should be followed per institutional guidelines, and unscheduled assessments should be performed when clinically indicated, as determined by the investigator. Refer to the Study Reference Manual for specific details and guidance related to additional CTX110 infusions.

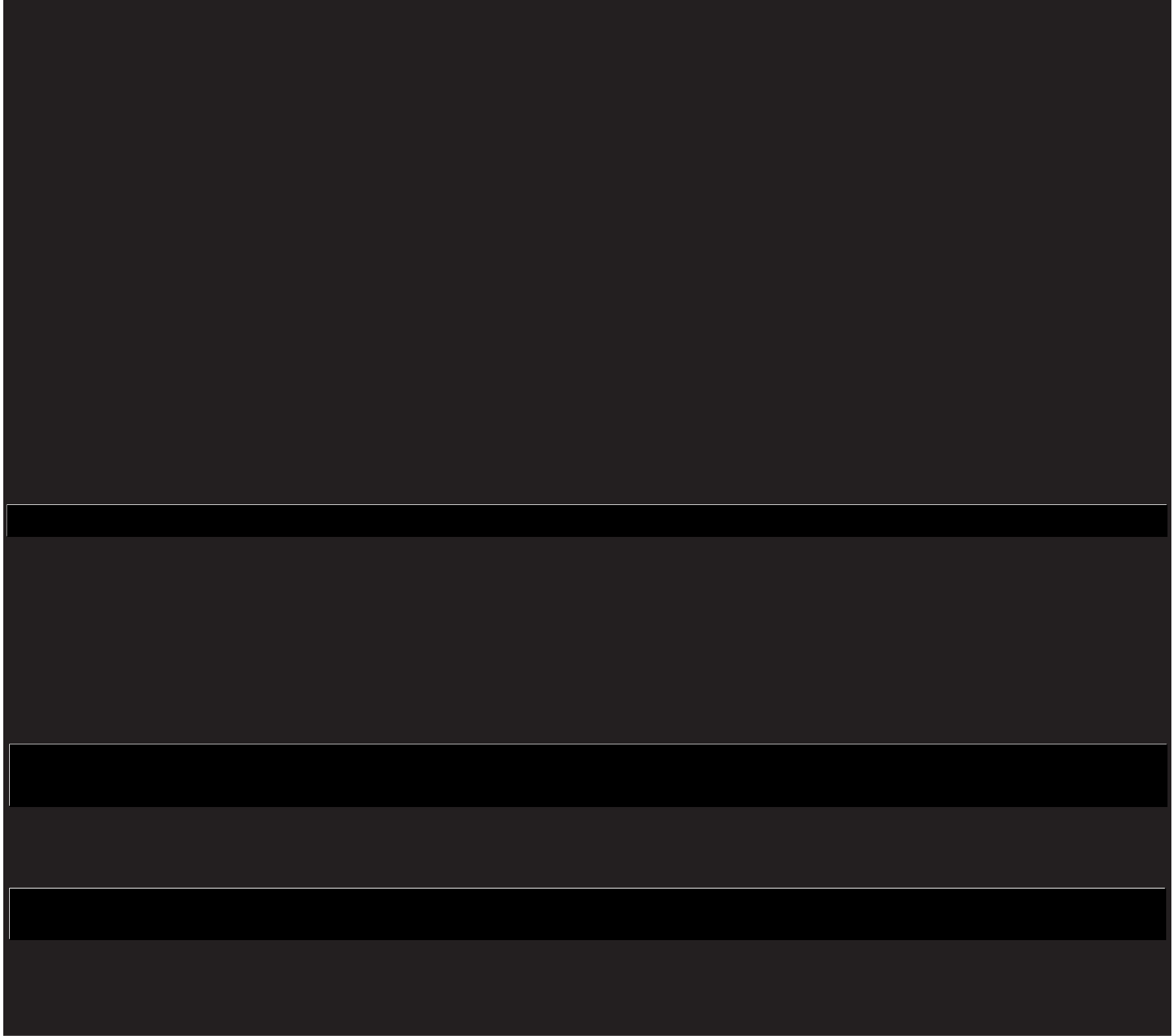
Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

For the purposes of this protocol, there is no Day 0. All visit dates and windows are to be calculated using Day 1 as the date of first CTX110 infusion.

Table 16: Phase 1 Schedule of Assessments (Screening to Month 24)

Study Stage	Screening (Stage 1)[1]	Treatment (Stage 2)			Follow-up (Stage 3)															
Day		D −10 to D−6[2]	D −5 to D−3	D1[3]	D2	D3 ±1d	D5 ±2d	D8 ±2d	D10 ±2d	D14 ±2d	D21 ±2d	D28 ±4d	M2 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	M15 ±14d	M18 ±14d	M24 ±21d
Informed consent	X																			
Confirm eligibility[4]	X	X	X	X								X								
Enrollment	X																			
Medical history[5]	X																			
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height, weight[7]	X	X	X	X				X		X		X	X	X	X	X	X	X	X	X
Pregnancy test[8]	X	X	X																	
ECOG status	X			X								X		X						
Brain MRI	X																			
Lumbar puncture[9]	X																			
Echocardiogram	X																			
12-lead ECG[10]	X	X	X	X								X								
ICE assessment[11]	X			X	X	X	X	X				X								
Patient-reported outcomes[12]	X			X								X		X	X	X	X		X	X
Concomitant meds[13]	Continuous																			
Adverse events[14]	Continuous																			
Hospital utilization			Continuous																	
Treatment																				

Study Stage	**Screening (Stage 1)[1]**	**Treatment (Stage 2)**			**Follow-up (Stage 3)**														
Day		**D −10 to D−6[2]**	**D −5 to D−3**	**D1[3]**	**D2**	**D3 ±1d**	**D5 ±2d**	**D8 ±2d**	**D10 ±2d**	**D14 ±2d**	**D21 ±2d**	**D28 ±4d**	**M2 ±7d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±14d**	**M15 ±14d**	**M18 ±14d**	**M24 ±21d**
Daratumumab[15]		X										X	X						
LD chemotherapy[16]			X[17]									X[18]							
CTX110 infusion [18,19]				X[17]								X[18]							
NHL Disease Response/Assessment (Central and Local)																			
PET scan/CT with IV contrast[20]	X											X		X[21]	X	X	X		X	X
BM aspirate/ biopsy[22]	X											X								
Tumor biopsy/pathology[23]	X[24]											X[23]								
Adult B Cell ALL Disease Response/Assessment																			
BM biopsy and aspirate (central and local)[21]	X											X	X[25]	X	X		X[26]			
BCR-ABL1 in peripheral blood (if Ph+)	X											X	X[25]	X	X		X[26]			
Imaging for extramedullary disease (if applicable)	X											X[27]								
Post-screening lumbar puncture												X[28]								
Peripheral blood chimerism (local)[29]	X																			



Ab: antibody; AE: adverse event; AESI: adverse event of special interest; ALL: acute lymphoblastic leukemia; B-ALL: B cell acute lymphoblastic leukemia; BM: bone marrow: CBC: complete blood count; CNS: central nervous system; CR: complete response; CRP: C-reactive protein; CRS: cytokine release syndrome; CT: computed tomography; D or d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV-1/-2: human immunodeficiency virus type 1 or 2; HLH: hemophagocytic lymphohistiocytosis; HSCT: hematopoietic stem cell transplant; ICE: immune effector cell–associated encephalopathy; IPI: International Prognostic Index; IV: intravenously; LD: lymphodepleting; LP: lumbar puncture; M: month; MRD: minimal residual disease; MRI: magnetic resonance imaging; NHL: non-Hodgkin lymphoma; PCR: polymerase chain reaction; PET: positron emission tomography; Ph+: Philadelphia chromosome-positive; PK: pharmacokinetic(s); PRO: patient-reported outcome; SAE: serious adverse event; SC: subcutaneous; SD: stable disease; [redacted]
Note: Study visits **cannot** be combined, even if visit windows allow overlap (e.g., D3 ±1 day could overlap with D2 or D5 ±2 days, but separate visits are required for D2, D3, and D5 visits.)
Note: Certain assessments for visits after D8 may be performed as in-home or alternate-site visits. Assessments include hospital utilization, changes in health and/or changes in medications, body system assessment, vital signs, weight, PRO questionnaire distribution, and blood sample collections for local and central laboratory assessments.

[1.] Screening assessments completed up to 14 days after informed consent. Subjects allowed 1-time rescreening within 3 months of initial consent, or longer if specific approval is obtained from the medical monitor.
[2.] Only for Cohort C. All procedures will be performed prior to daratumumab administration.
[3.] All baseline assessments on Day 1 are to be performed prior to CTX110 infusion unless otherwise specified; refer to Laboratory Manual for details.
[4.] Study eligibility to be confirmed before enrollment. Eligibility for treatment based on clinical status to be confirmed before start of LD chemotherapy (Cohorts A, B, and D) or daratumumab (Cohort C) and before CTX110 infusion (see Sections 5.1, 5.2, and 5.3).
[5.] Includes complete surgical and cardiac history.
[6.] Includes sitting blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature.
[7.] Height at screening only.
[8.] For female subjects of childbearing potential. Serum pregnancy test at screening. Serum or urine pregnancy test within 72 hours before start of LD chemotherapy (Cohorts A, B, and D) or daratumumab (Cohort C) or additional CTX110 infusions (Cohorts A, B, C2, and D) when administered without daratumumab or LD chemotherapy.
[9.] Mandatory for Cohort D subjects. For Cohorts A, B, and C: LP at screening for subjects with high risk for CNS involvement (e.g., high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements or double-expressor lymphoma, subjects with testicular involvement of lymphoma, or subjects with high-risk CNS IPI score). For LPs performed during neurotoxicity, samples should be sent to central laboratory for CTX110 PK and [redacted]
[10.] Prior to daratumumab infusion (Cohort C), prior to LD chemotherapy (Cohorts A, B, and D), and prior to CTX110 infusion (all cohorts).
[11.] On Day 1 prior to CTX110 administration, then all listed time points. If CNS symptoms persist, ICE assessment should continue to be performed approximately every 2 days until symptom resolution to grade 1 or baseline.
[12.] PRO surveys should be administered before any visit-specific procedures are performed. See Section 7.2.13.
[13.] All concomitant medications will be collected ≤3 months post-CTX110, after which only select concomitant medications will be collected (Section 5.4.1).
[14.] Collect all AEs from informed consent to 3 months after each CTX110 infusion and collect only SAEs, AESIs, and nonserious AEs related to LD chemotherapy from 3 months after last CTX110 infusion through Month 24 visit. After Month 24 to Month 60 or after a subject starts a new [redacted] anytime on the study, only SAEs and AESIs related to LD chemotherapy, study procedure, or CTX110 and new malignancies will be reported. See Section 8.7, Table 21 for details.
[15.] Cohort C only: 1 dose of daratumumab 16 mg/kg IV or 1800 mg SC administered ≥1 day prior to starting LD chemotherapy and within 10 days prior to CTX110 infusion (Section 5.1). The first 16 mg/kg IV dose may be split (to 8 mg/kg) over 2 consecutive days. For subjects in Subcohort C1 who achieve SD or better on Day 28, 2 additional doses of daratumumab (16 mg/kg IV or 1800 mg SC) will be administered at the Day 28 (± 4 days) and Month 2 (± 4 days)

visits. Confirmation of SD state based on PET/CT scan measurement will be required before repeat dosing with daratumumab. If a subject experiences severe or unmanageable AEs with prior daratumumab doses, redosing with daratumumab will not be permitted.

16. For first CTX110 infusion, start LD chemotherapy within 7 days of study enrollment. After completion of LD chemotherapy, ensure washout period of ≥48 hours (but ≤7 days) before CTX110 infusion. Physical exam, weight, and coagulation laboratories performed prior to first dose of LD chemotherapy. Vital signs, CBC, clinical chemistry, and AEs/concomitant medications assessed and recorded daily (i.e., 3 times) during LD chemotherapy.
17. This study will allow for a second CTX110 infusion for subjects in Cohorts A, B, C2, D1, and D2 per the criteria in Section 5.3.1.3 and Section 5.3.1.4. Subjects who receive the second CTX110 infusion should be followed per the schedule of assessments consistent with the initial dosing. All procedures (screening through Day 28) must be repeated, with exceptions for screening assessments specified in Section 5.3.1.3 and Section 5.3.1.4. Month 2 visit procedures do not need to be repeated if they have been performed as part of a visit occurring within 28 days of the second CTX110 infusion.
18. A second infusion of CTX110 on Day 35 (-7 days/+21 days) administered with LD chemotherapy for subjects who achieve objective response at Day 28 assessment. The second infusion may be administered without LD chemotherapy if subject is experiencing significant cytopenias (see Section 5.3.1.3.1). In addition, this study will allow for a second course of treatment with a single CTX110 infusion with LD chemotherapy after PD. See Section 5.3.1 for the eligibility and additional considerations for screening assessments. All subjects will be followed according to Table 16 after additional CTX110 infusions.
19. For first CTX110 infusion and additional CTX110 infusions with LD chemotherapy, CTX110 will be administered 48 hours to 7 days after completion of LD chemotherapy.
20. Baseline disease assessment (PET scan/CT of diagnostic quality for subjects with NHL or BM biopsy with imaging for extra medullary disease (if applicable) for subjects with B-ALL) to be performed within 28 days prior to CTX110 infusion. BM for B-ALL may be assessed locally and centrally at any time prior to the 14-day window for screening, with appropriate consent. In Subcohort D2, if MRD results are pending at the time of enrollment, it is acceptable for eligibility purposes to enroll based on BM performed during screening that confirms BM blast count <5% accompanied by qualifying MRD results performed within the past 3 months. MRI with contrast allowed if CT is clinically contraindicated, or as required by local regulation. Additional imaging at Month 2 allowed per investigator discretion.
21. For all subjects who receive a second CTX110 infusion on Day 35 (-7 days/+21 days), a PET/CT scan is required 28 days after that infusion to assess efficacy. It is permissible for that scan to replace the Month 3 imaging.
22. To be performed ± 5 days of visit date. BM at Day 28 is required for NHL subjects with BM involvement at screening. Additional BM biopsy and aspirate must be performed to confirm CR as part of disease evaluation for NHL subjects with BM involvement at screening and to evaluate CTX110 trafficking. BM biopsy and aspirate may also be performed at time of disease relapse. Samples from all BM biopsy and aspirate should be sent for CTX110 PK and [redacted] If HLH is suspected, BM biopsy and aspirate to be performed as specified in Section 6.2.7.
23. Optional: For subjects who have disease amenable to biopsy and who provide separate consent. To be performed ± 5 days of visit date.
24. It is preferred that subjects undergo tumor biopsy during screening. However, if a biopsy of relapsed/refractory disease was performed within 3 months prior to enrollment and after the most recent line of therapy, archival tissue may be used (see Laboratory Manual for details). If relapse occurs on study, every attempt should be made to obtain biopsy of relapsed tumor and send to central pathology. Tumor biopsy refers to tissue other than bone marrow.
25. Assessments optional at Month 2 to confirm CR if not achieved at Month 1.
26. For Subcohort D2 only.
27. If applicable, imaging for extramedullary disease at baseline, Day 28, and at subsequent visits as clinically indicated or to confirm CR.
28. For subjects with baseline CNS disease: to confirm CR and when clinically indicated.
29. To be performed only in subjects who have received prior allogeneic HSCT.
30. All local and central laboratory assessments should be performed prior to dosing, unless otherwise specified. Assessments at Month 6 or later may be delayed or moved ahead of the visit window to accommodate holidays, vacations, and unforeseen delays.
31. For subjects experiencing grade ≥3 neutropenia, thrombocytopenia, or anemia that has not resolved within 28 days of CTX110 infusion, a CBC with differential must be performed more frequently until resolution to grade ≤2 or administration of a new systemic [redacted] They should be performed weekly until 3 months after each CTX110 infusion and then should be performed at least monthly.

[32] Infectious disease testing (HIV-1, HIV-2, HCV antibody/PCR, HBV surface antigen, HBV surface antibody, HBV core antibody) ≤45 days of enrollment may be considered for subject eligibility.

[33] [redacted] assessment at screening, before daratumumab infusion (Cohort C), before start of first day of LD chemotherapy (Cohorts A, B, and D), before CTX110 infusion (all cohorts), then all listed time points. [redacted]

[34] Blood type and [redacted] prescribing information to prevent interference with blood compatibility testing for subjects in Cohort C after cohort allocation is confirmed, and before daratumumab infusion.

[35] Samples for CTX110 PK should be sent from any LP, BM aspirate, or tissue biopsy performed following CTX110 infusion. In subjects experiencing signs or symptoms of CRS, neurotoxicity, or suspected HLH, additional blood samples should be drawn at intervals outlined in the laboratory manual. Samples for CRS PK should only be collected between scheduled visits. If samples are already being collected as part of a scheduled visit, no additional samples are required to be collected for CRS PK on the same day of the scheduled visit.

[redacted]

[37] Two samples collected on Day 1: One pre–CTX110 infusion and one 20 (±5) minutes after the end of CTX110 infusion.

[redacted]

[41] Prior to first day of LD chemotherapy only.

Table 17: Phase 2 Schedule of Assessments (Screening to Month 24)

Study Stage	**Screening[1]**	**Treatment**		**Follow-up**														
Day		**D −5 to D−3**	**D1[(2)]**	**D2**	**D3 ±1d**	**D5 ±2d**	**D8 ±2d**	**D10 ±2d**	**D14 ±2d**	**D21 ±2d**	**D28 ±4d**	**M2 ±7d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±14d**	**M15 ±14d**	**M18 ±14d**	**M24 ±21d**
Informed consent	X																		
Confirm eligibility[3]	X																		
Enrollment	X																		
Medical history[4]	X																		
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Stage	**Screening**[1]	**Treatment**		**Follow-up**															
Day		**D −5 to D−3**	**D1**[(2)]	**D2**	**D3 ±1d**	**D5 ±2d**	**D8 ±2d**	**D10 ±2d**	**D14 ±2d**	**D21 ±2d**	**D28 ±4d**	**M2 ±7d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±14d**	**M15 ±14d**	**M18 ±14d**	**M24 ±21d**
Height, weight[6]	X	X	X				X		X		X	X	X	X	X	X	X	X	X
Pregnancy test[7]	X	X																	
ECOG status	X		X								X		X						
Brain MRI	X																		
Lumbar puncture[8]	X																		
Echocardiogram	X																		
12-lead ECG[9]	X	X	X								X								
ICE assessment[10]	X		X	X	X	X	X				X								
Patient-reported outcomes[11]	X		X								X		X	X	X	X		X	X
Concomitant meds[12]	Continuous																		
Adverse events[13]	Continuous																		
Hospital utilization		Continuous																	
Treatment																			
LD chemotherapy[14]		X[15]									X[16]								
CTX110 infusion[14, 16, 17]			X[15]								X[16]								
Disease Response/Assessment (Central and Local)																			
PET scan/CT with IV contrast[18]	X										X		X[19]	X	X	X		X	X
BM aspirate/ biopsy[20]	X										X								

Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV-1/-2: human immunodeficiency virus type 1 or 2; HLH: hemophagocytic lymphohistiocytosis; HSCT: hematopoietic stem cell transplant; ICE: immune effector cell–associated encephalopathy; IPI: International Prognostic Index; IV: intravenously; LD: lymphodepleting; LP: lumbar puncture; M: month; MRD: minimal residual disease; MRI: magnetic resonance imaging; PCR: polymerase chain reaction; PET: positron emission tomography; Ph+: Philadelphia chromosome-positive; PK: pharmacokinetic(s); PRO: patient-reported outcome; SAE: serious adverse event; [redacted]

Note: Study visits **cannot** be combined, even if visit windows allow overlap (e.g., D3 ±1 day could overlap with D2 or D5 ±2 days, but separate visits are required for D2, D3, and D5 visits.)

Note: Certain assessments for visits after D8 may be performed as in-home or alternate-site visits. Assessments include hospital utilization, changes in health and/or changes in medications, body system assessment, vital signs, weight, PRO questionnaire distribution, and blood sample collections for local and central laboratory assessments.

1. Screening assessments completed up to 14 days after informed consent. Subjects allowed 1-time rescreening within 3 months of initial consent, or longer if specific approval is obtained from the medical monitor.
2. All baseline assessments on Day 1 are to be performed prior to CTX110 infusion unless otherwise specified; refer to Laboratory Manual for details.
3. Study eligibility to be confirmed before enrollment. Eligibility for treatment based on clinical status to be confirmed before start of LD chemotherapy and before CTX110 infusion (see Sections 5.2 and 5.3).
4. Includes complete surgical and cardiac history.
5. Includes sitting blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature.
6. Height at screening only.
7. For female subjects of childbearing potential. Serum pregnancy test at screening. Serum or urine pregnancy test within 72 hours before start of LD chemotherapy or additional CTX110 infusions when administered without LD chemotherapy.
8. LP at screening for subjects with high risk for CNS involvement (e.g., high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements or double-expressor lymphoma, subjects with testicular involvement of lymphoma, or subjects with high-risk CNS IPI score). For LPs performed during neurotoxicity, samples should be sent to central laboratory for CTX110 PK and [redacted] whenever possible.
9. Prior to LD chemotherapy and prior to CTX110 infusion.
10. On Day 1 prior to CTX110 administration, then all listed time points. If CNS symptoms persist, ICE assessment should continue to be performed approximately every 2 days until symptom resolution to grade 1 or baseline.
11. PRO surveys should be administered before any visit-specific procedures are performed. See Section 7.2.13.
12. All concomitant medications will be collected ≤3 months post-CTX110, after which only select concomitant medications will be collected (Section 5.4.1).
13. Collect all AEs from informed consent to 3 months after each CTX110 infusion and collect only SAEs, AESIs, and nonserious AEs related to LD chemotherapy from 3 months after last CTX110 infusion through Month 24 visit. After Month 24 to Month 60 or after a subject starts a new [redacted] anytime on the study, only SAEs and AESIs related to LD chemotherapy, study procedure, or CTX110 and new malignancies will be reported. See Section 8.7, Table 21 for details.
14. For first CTX110 infusion, start LD chemotherapy within 7 days of study enrollment. After completion of LD chemotherapy, ensure washout period of ≥48 hours (but ≤7 days) before CTX110 infusion. Physical exam, weight, and coagulation laboratories performed prior to first dose of LD chemotherapy. Vital signs, CBC, clinical chemistry, and AEs /concomitant medications assessed and recorded daily (i.e., 3 times) during LD chemotherapy.
15. Subjects will receive a second CTX110 infusion if they meet the criteria in Section 5.3.1.3 and Section 5.3.1.4. All procedures (screening through Day 28) must be repeated, with exceptions for screening assessments specified in Section 5.3.1.3 and Section 5.3.1.4. Month 2 visit procedures do not need to be repeated if they have been performed as part of a visit occurring within 28 days of the second CTX110 infusion.
16. A second infusion of CTX110 on Day 35 (-7 days/+21 days) will be administered with LD chemotherapy for subjects who achieve an objective response at the Day 28 assessment. The second infusion may be administered without LD chemotherapy if subject is experiencing significant cytopenias (see Section 5.3.1.3.1). In addition, a second course of treatment with a single CTX110 infusion with LD chemotherapy may be administered after PD for subjects

who achieve a response to the first course of treatment. See Section 5.3.1 for the eligibility and additional considerations for screening assessments. All subjects will be followed according to Table 17 after additional CTX110 infusions.

[17.] For first CTX110 infusion and additional CTX110 infusions with LD chemotherapy, CTX110 will be administered 48 hours to 7 days after completion of LD chemotherapy.

[18.] Baseline disease assessment (PET scan/CT of diagnostic quality to be performed within 28 days prior to CTX110 infusion. MRI with contrast allowed if CT is clinically contraindicated, or as required by local regulation. Additional imaging at Month 2 allowed per investigator discretion.

[19.] For all subjects who receive a second CTX110 infusion on Day 35 (-7 days/+21 days), a PET/CT scan is required 28 days after that infusion to assess efficacy. If that PET/CT scan from the second CTX110 infusion occurs within 14 days of the initial Month 3 scan (including window), it is permissible for that scan to replace the Month 3 imaging.

[20.] To be performed ± 5 days of visit date. BM at Day 28 is required for subjects with BM involvement at screening. Additional BM biopsy and aspirate must be performed to confirm CR as part of disease evaluation for subjects with BM involvement at screening and to evaluate CTX110 trafficking. BM biopsy and aspirate may also be performed at time of disease relapse. Samples from all BM biopsy and aspirate should be sent for CTX110 PK and [redacted] If HLH is suspected, BM biopsy and aspirate to be performed as specified in Section 6.2.7.

[21.] Optional: For subjects who have disease amenable to biopsy and who provide separate consent. To be performed ± 5 days of visit date.

[22.] It is preferred that subjects undergo tumor biopsy during screening. However, if a biopsy of relapsed/refractory disease was performed within 3 months prior to enrollment and after the most recent line of therapy, archival tissue may be used (see Laboratory Manual for details). If relapse occurs on study, every attempt should be made to obtain biopsy of relapsed tumor and send to central pathology. Tumor biopsy refers to tissue other than bone marrow.

[23.] All local and central laboratory assessments should be performed prior to dosing, unless otherwise specified. Assessments at Month 6 or later may be delayed or moved ahead of the visit window to accommodate holidays, vacations, and unforeseen delays.

[24.] For subjects experiencing grade ≥3 neutropenia, thrombocytopenia, or anemia that has not resolved within 28 days of CTX110 infusion, a CBC with differential must be performed more frequently until resolution to grade ≤2 or administration of a new systemic [redacted] They should be performed weekly until 3 months after each CTX110 infusion and then should be performed at least monthly.

[25.] Infectious disease testing (HIV-1, HIV-2, HCV antibody/PCR, HBV surface antigen, HBV surface antibody, HBV core antibody) ≤45 days of enrollment may be considered for subject eligibility.

[26.] [redacted] assessment at screening, before start of first day of LD chemotherapy, before CTX110 infusion, then all listed time points. [redacted]

[27.] Samples for CTX110 PK should be sent from any LP, BM aspirate, or tissue biopsy performed following CTX110 infusion. In subjects experiencing signs or symptoms of CRS, neurotoxicity, or suspected HLH, additional blood samples should be drawn at intervals outlined in the laboratory manual. Samples for CRS PK should only be collected between scheduled visits. If samples are already being collected as part of a scheduled visit, no additional samples are required to be collected for CRS PK on the same day of the scheduled visit.

[redacted]

[29.] Two samples collected on Day 1: One pre-CTX110 infusion and one 20 (±5) minutes after the end of CTX110 infusion.

[30.] [redacted] samples should be collected daily for the duration of CRS. Day 1 samples to be collected prior to CTX110 infusion. During neurotoxicity and suspected HLH [redacted] will be collected (see Laboratory Manual for specific information). Samples for CRS should only be collected between scheduled visits. If samples are already being collected as part of a scheduled visit, no additional samples are required to be collected for CRS on the same day of the scheduled visit.

[redacted]

[32.] Prior to first day of LD chemotherapy only.

Table 18: Phase 1 and Phase 2 Schedule of Assessments (Months 30-60)

Assessments	M30 (± 21 days)	M36 (± 21 days)	M42 (± 21 days)	M48 (± 21 days)	M54 (± 21 days)	M60 (± 21 days)	Progressive Disease	Secondary Follow-Up[1]
Vital signs[2]	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X
Concomitant medications[3]	X	X	X	X	X	X	X	X
Survival status	X	X	X	X	X	X	X	X
Disease assessment[4]	X	X	X	X	X	X	X	
Tumor biopsy[4]							X	
CBC with differential[5]	X	X	X	X	X	X	X	X
Serum chemistry[5]	X	X	X	X	X	X	X	X
Immunoglobulins[5,6]	X	X	X	X	X	X	X	
[redacted]								
CTX110 persistence (central)[6,7]		X		X		X	X	X
[redacted]								
Patient-reported outcomes	X	X	X	X	X	X	X	
Adverse events[8]	X	X	X	X	X	X	X	X
[redacted]								

Ab: antibody; AE: adverse event; AESI: adverse event of special interest; ALL: acute lymphoblastic leukemia; BM: bone marrow; CBC: complete blood count; CRS: cytokine release syndrome; CT: computed tomography; GvHD: graft vs host disease; HLH: hemophagocytic lymphohistiocytosis; LD: lymphodepleting; M: month; NHL: non-Hodgkin lymphoma; PET: positron emission tomography; PK: pharmacokinetic; PRO: patient-reported outcome; SAE: serious adverse event; [redacted]

NOTE: Certain assessments for visits after Day 8 may be performed as in-home or alternate-site visits. Assessments include hospital utilization, changes in health and/or changes in medications, body system assessment, vital signs, weight, PRO questionnaire distribution, and blood sample collections for local and central laboratory assessments.

[1.] Subjects with progressive disease or who receive a subsequent line of [redacted] will discontinue the normal schedule of assessments and attend annual study visits. The first secondary follow-up visit will occur 1 year (±6 weeks) after the progressive disease visit. Survival status, AEs, and [redacted] should be assessed every 6 months during secondary follow-up (by telephone, medical record review, or search of publicly available records [see Section 7.1.5] for time points that fall between scheduled visits). Subjects who have entered secondary follow-up in this protocol can roll over into the CRISPR

long-term follow-up protocol if the long-term follow-up protocol is approved and activated at the investigative site. Subjects who partially withdraw consent will undergo these procedures at minimum. 100-day transplant-related outcomes will be collected from subjects with B cell ALL who undergo stem cell transplant. These may include survival rate, nonrelapse survival rate, and rate of GvHD.

[2.] Includes temperature, blood pressure, pulse rate, and respiratory rate.

[3.] Only select concomitant medications will be collected (Section 5.4.1).

[4.] Disease assessment will consist of investigator review of physical exam, CBC, clinical chemistry, and lactate dehydrogenase for NHL subjects, and of physical exam, CBC with differential, and clinical chemistry for B cell ALL. NHL subjects with suspected malignancy will undergo PET/CT imaging and/or a BM biopsy to confirm relapse. B cell ALL subjects with suspected malignancy will undergo bone marrow biopsy and aspirate, imaging of extramedullary lesions, and lumbar puncture for disease assessment. Every attempt should be made to obtain a biopsy of the relapsed tumor in subjects who progress.

[5.] Assessed at local laboratory [redacted]

Samples for CTX110 PK analysis should be sent to the central laboratory from any lumbar puncture, BM biopsy, or tissue biopsy performed following CTX110 infusion.

[8.] SAEs, AESIs and nonserious AEs related to LD chemotherapy, study procedure, or CTX110 should be reported until last study visit. Only SAEs and AESIs related to LD chemotherapy, study procedure, or CTX110 will be reported after Month 24 to Month 60 or if a subject starts new [redacted] anytime ≥3 months after CTX110 infusion. See Section 8.7, Table 21 for details.

7.1. Subject Screening, Enrollment, and Withdrawal

7.1.1. Subject Screening and Enrollment

Investigators will keep a log of all potential subjects reviewed and evaluated for study participation. The screening log will capture limited information such as date of screening, date of enrollment, and reason why a subject failed screening. If at any time in the screening period a subject fails to meet the eligibility criteria, the subject will be designated a screen failure.

The screening period begins on the date that the subject informed consent form (ICF) and continues through confirmation of eligibility and enrollment into the study. Once informed consent has been obtained, the subject will be screened to confirm study eligibility as outlined in the schedule of assessments (Table 16 and Table 17). Screening assessments are to be completed up to 14 days after a subject signs the ICF.

After screening is completed, a subject is deemed enrolled in the study upon the principal investigator's confirmation of eligibility, and the sponsor's approval of enrollment. Subjects should start LD chemotherapy within 7 days after study enrollment.

Subjects will be allowed a one-time rescreening, which may take place within 3 months of the initial consent.

7.1.2. Subject Identification

A unique subject number will be assigned when an individual subject signs the study ICF. Subjects will be identified by a subject number consisting of:

> Last 3 digits of protocol number (001), 3-digit site number, sequential 3-digit subject number (e.g., 001-XXX-YYY)

Subject numbers will be assigned via an interactive web response system. Once a number is assigned, it cannot be reassigned to a different subject. Rescreened participants will keep the same participant number assigned during the initial screening process.

7.1.3. Assignment of Subjects to Treatment Cohorts

Cohorts A, B, and C will comprise subjects with NHL, including DLBCL NOS, high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, transformed FL, grade 3b FL, and PMBCL. Enrollment and allocation of subjects to Cohorts A, B, and C will be at the sponsor's discretion. Subjects with B cell ALL will be exclusively assigned to Cohort D in parallel with other cohorts. The starting dose for escalation will be selected separately for each cohort and will reflect the cumulative safety data across all cohorts for each study population (NHL, adult B cell ALL). Whenever escalation begins in a new cohort, the sponsor and SRC will discuss and agree on the starting dose level, which will not exceed the highest dose level cleared in Cohort A. There will be a dose limit of [redacted] TCR^+ cells/kg for all dose levels, which will determine the minimum weight for dosing. Dosing will be staggered as described in Section 4.1.4.

7.1.4. Replacement of Subjects

During Phase 1 Part A, subjects who withdraw or are lost to follow-up before completing the DLT evaluation period will be replaced. In addition, during Part A, if LD chemotherapy is delayed more than 30 days or the subjects starts [redacted] the subject will be replaced. During Part B, subjects who withdraw from the study before receiving LD chemotherapy in Cohorts A, B, or D, or before daratumumab in Cohort C may be replaced. Subjects who discontinue from the study at any other time for any other reason will not be replaced.

7.1.5. Subject Withdrawal or Removal

Subjects may voluntarily withdraw from the study at any time. Withdrawal of full consent means that the subject does not wish to receive further protocol-required therapy, undergo study procedures, or continue any further study follow-up. The sponsor will be notified of all study withdrawals. Subject data and samples collected up to the date of withdrawal of consent will be retained and included in the analyses. Where permitted by local regulations, publicly available data (e.g., death records) may be included after withdrawal of consent.

Subjects can also decide to stop receiving selected protocol assessments, procedures, and/or treatments but otherwise continue to participate in the study (i.e., partial withdrawal of consent). In this case, the site and subject should discuss and agree to a plan for further study participation and document this plan in source documents, clearly specifying the protocol activities that will continue to be performed.

The investigator will specify reason for removal from the study as follows:

- Subject withdrawal of consent
- Investigator decision
- Loss to follow-up
- Death

For subjects who are lost to follow-up, the investigator should attempt to search publicly available records (where permitted and allowed by local law) to ascertain survival status. Attempts should also be made to collect information related to hospitalizations from other sources for the duration of the study.

Subjects who enter secondary follow-up due to disease progression, investigator decision / start of new [redacted] should attend annual visits through Month 60 to collect safety inform [redacted] in Table 17 under secondary follow-up visit. Subjects who have entered secondary follow-up in this protocol can roll over into the CRISPR long-term follow-up protocol if the long-term follow-up protocol is approved and activated at the investigative site.

7.2. Study Assessments

Refer to the schedule of assessments in Table 16, Table 17, and Table 18 for the timing of the required procedures.

7.2.1. Informed Consent

The investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

Whenever important new information becomes available that may be relevant to the subject's consent, the written ICF and any other written information provided to subjects will be revised by the sponsor or designee and be submitted again to the institutional review board (IRB)/ethics committee (EC) for review and favorable opinion. The agreed upon, revised information will be provided to each subject in the study for signing and dating. The investigator will explain the changes to the previous version.

7.2.2. Medical History

Demographic data will be collected. Medical history, including a full history of the subject's disease, previous cancer treatments, and response to treatment from date of diagnosis will be obtained. Cardiac, neurological, and surgical history will be obtained.

For trial entry, all subjects must fulfill all inclusion criteria described in Section 3.1, and have none of the exclusion criteria described in Section 3.2.

7.2.3. Physical Exam

Physical examination, including examination of major body systems, including general appearance, skin, neck, head, eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system, will be performed at every study visit and the results documented. Changes noted from the exam performed at screening will be recorded as an AE.

7.2.4. Vital Signs, Including Height and Weight

Vital signs will be recorded at every study visit and include sitting blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry, temperature, and height. Weight will be obtained according to the schedule in Table 16 and Table 17, and height will only be obtained at screening.

7.2.5. Pregnancy Test

Female subjects of childbearing potential (women who have reached menarche or women who have not been postmenopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone a sterilization procedure [hysterectomy or bilateral oophorectomy]) must have a serum pregnancy test performed at the time of screening, and a serum or urine pregnancy test within 72 hours of beginning LD chemotherapy

(Cohorts A, B, and D), daratumumab (Cohort C), or additional infusion of CTX110, if applicable, when administered without daratumumab or LD chemotherapy.

Contraception requirements for both male and female subjects are outlined in Appendix C.

7.2.6. ECOG Performance Status

Performance status will be assessed at the screening, CTX110 infusion (Day 1), Day 28, and Month 3 visits. Performance status will be assessed using the ECOG scale to determine the subject's general well-being and ability to perform activities of daily life (Appendix B).

7.2.7. Echocardiogram

A transthoracic cardiac echocardiogram (for assessment of left ventricular ejection fraction) will be performed and read by trained medical personnel at screening to confirm eligibility. Additional cardiac assessment is recommended during grade 3 or 4 CRS for all subjects who require >1 fluid bolus for hypotension, who are transferred to the intensive care unit for hemodynamic management, or who require any dose of vasopressor for hypotension (Brudno and Kochenderfer, 2016).

7.2.8. Electrocardiogram

Twelve (12)-lead electrocardiograms (ECGs) will be obtained during screening, prior to daratumumab infusion (Cohort C), prior to LD chemotherapy on the first day of treatment (Cohorts A, B, and D), prior to CTX110 administration on Day 1 (all cohorts), and on Day 28. QTc and QRS intervals will be determined from ECGs. Additional ECGs may be obtained at the investigator's discretion.

7.2.9. NHL Tumor Pathology

Histopathological diagnosis of NHL subtype will be based on local laboratory assessment. It is preferred that subjects undergo tumor biopsy during screening. However, if a biopsy of relapsed/refractory disease was performed after completion of last line of therapy and within 3 months prior to enrollment, archival tissue may be used. Bone biopsies and other decalcified tissues are not acceptable due to interference with downstream assays.

Portions of the tissue biopsy will be submitted to a central laboratory for analysis. Requirements for tissue preparation and shipping can be found in the Laboratory Manual. If archival tissue is of insufficient volume or quality to fulfill central laboratory requirements, a biopsy during screening must be performed. Archival tumor tissue samples may be analyzed for markers of aggressive NHL (e.g., *MYC*, *BCL2*, *BCL6*) as well as immune markers in the tumor and surrounding microenvironment (e.g., programmed cell death protein 1, programmed cell death-ligand 1).

If relapse occurs on study, every attempt should be made to obtain biopsy of relapsed tumor and send to central pathology. Tumor biopsy refers to tissue other than bone marrow (see Table 16 and Table 17).

7.2.10. Brain MRI

To rule out CNS metastasis, a brain MRI will be performed during the screening. Requirements for the acquisition, processing, and transfer of this MRI will be outlined in the Imaging Manual.

7.2.11. Lumbar Puncture

A lumbar puncture will be performed at screening according to institutional standard procedures in all subjects with adult B cell ALL (Cohort D) to assess presence of malignancy. For Cohorts A, B, and C, lumbar puncture at screening will be performed in subjects at high risk for CNS involvement. These include subjects with high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement or double-expressor lymphoma; subjects with testicular involvement of lymphoma; or subjects with high-risk scores on the CNS International Prognostic Index, a tool used to estimate risk of CNS relapse/progression in patients with DLBCL treated with R-CHOP (Schmitz et al., 2016).

If clinically feasible, for lumbar punctures performed during neurotoxicity, [redacted] and for presence of CTX110 (by PCR). Whenever lumbar puncture is performed in the setting of neurotoxicity evaluation, in addition to the standard panel performed at the site (which should include at least cell count, Gram stain, and *Neisseria meningitidis*) the following viral panel must be performed (see Section 6.2.5): CSF PCR analysis for HSV-1 and -2, enterovirus, VZV, CMV, and HHV-6.

Results of viral panel should be available within 5 business days from draw to support appropriate management of a subject.

[redacted]

A lumbar puncture on Day 28 for analysis of CSF may also be required to confirm CR after CTX110 administration in subjects with B cell ALL with CNS disease at baseline (Table 16).

7.2.12. Immune Effector Cell–associated Encephalopathy (ICE) Assessment

Neurocognitive assessment will be performed using the ICE assessment. The ICE assessment is a slightly modified version of the CARTOX-10 screening tool, which now includes a test for receptive aphasia. The ICE assessment (Table 10) examines various areas of cognitive function: orientation, naming, following commands, writing, and attention.

The ICE assessment will be performed at screening, before administration of CTX110 on Day 1, and on Days 2, 3, 5, 8, and 28. If a subject experiences CNS symptoms, the ICE assessment should continue to be performed approximately every 2 days until resolution of symptoms. To minimize variability, whenever possible the assessment should be performed by the same research staff member who is familiar with or trained in administration of the ICE assessment.

7.2.13. Patient-reported Outcomes

For Cohorts A, B, and C, 3 PRO surveys, the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System's Functional Assessment of Cancer Therapy (FACT)–specific subscale for lymphoma (FACT-Lym v 4.0), the Short Form Survey Instrument (SF-36 v 2.0), and EuroQoL Group 5-Dimension (EQ-5D-5L) questionnaire, and will be administered according to the schedule in Table 16 and Table 17. For Cohort D, FACT for leukemia

(FACT-Leu v4.0), and EQ-5D-5L will be administered. Questionnaires should be completed (self-administered in the language the subject is most familiar) before clinical assessments are performed.

FACT-Lym is a standardized tool based on the validated general FACT assessment in oncology, the FACT-G (Cella et al., 1993). The FACT-Lym evaluates the 4 domains of quality of life: physical, social/family, emotional, and functional well-being in the FACT-G, along with a 15-question subscale specific to lymphoma. The subscale component is designed to capture patient concerns and clinical issues specific to patients undergoing treatment for lymphoma (Cella et al., 2005).

The FACT-Leu is a standardized tool also based on the validated general FACT assessment in oncology, the FACT-G (Cella et al., 1993). In addition to the FACT-G subscales, it comprises a 17-question leukemia-specific subscale designed to capture concerns and symptoms specific to patients undergoing treatment for acute or chronic disease (Cella et al., 2012).

The SF-36 is a 36-item health survey assessing 8 facets of health: physical functionality, pain, activity limitation due to physical health problems, activity limitation from personal or emotional health issues, emotional well-being, social function, energy/fatigue, and perceptions of general health, as well as a single question that addresses the subject's perception of changes to his/her health (Ware and Sherbourne, 1992).

The EQ-5D-5L comprises a 5-item descriptive system questionnaire and a visual analogue scale (VAS). The descriptive system assesses health on the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with each dimension including 5 levels of severity: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS assesses self-rated health on a 20-cm vertical scale from 0 (worst imaginable health) to 100 (best imaginable health).

7.2.14. Hospitalizations and Health Care Resource Utilization

Data on hospitalization, including intensive care unit stay and outpatient day use, will be collected during the first 2 months after each CTX110 infusion.

7.2.15. PET/CT and Radiologic Disease Response Assessments for NHL

PET/CT scans of all sites of disease (including the neck, chest, abdomen, and pelvis) are required. The CT portion of PET/CT should be of diagnostic quality. MRI with contrast may be used when CT is clinically contraindicated or as required by local regulation. The baseline PET/CT must be performed within 28 days prior to administration of CTX110, and postinfusion scans will be conducted per the schedule of assessments in Table 16 and Table 17. If a subject has symptoms consistent with possible disease progression, an unscheduled PET/CT should be performed. Additional detail on imaging required for disease assessments can be found in the imaging manual.

For all subjects who receive a second CTX110 infusion on Day 35 (-7 days/+21 days), a PET/CT scan is required 28 days after that infusion to assess efficacy. It is permissible for that scan to replace the Month 3 imaging.

Requirements for the acquisition, processing, and transfer of scans will be outlined in the Imaging Manual. When possible, the imaging modalities, machines, and scanning parameters used to acquire PET/CT should be kept consistent during the study. All radiological images available for the site investigators will be transmitted by the sites to a central imaging vendor designated by the sponsor.

Tumor burden will be quantified at baseline according to Lugano criteria (Appendix A). Tumor burden assessments are to include the SPD calculated by aggregating the dimensions of each target lesion (nodal or extranodal) for a maximum of 6 target lesions, by multiplying the 2 longest perpendicular diameters of lesions. Target lesions should be selected from those with the largest size that can be reproducibly measured, representing overall tumor burden across multiple sites and organs.

Tumor response will be determined according to Lugano criteria (Appendix A) and will be assessed by both the local investigators and a central imaging review. The determination of study eligibility and decisions regarding subject management and disease progression will be made by the investigator. Postbaseline imaging will be compared against baseline imaging to determine a response; however, imaging indicative of progression may be compared against the nadir.

7.2.15.1. Imaging of Extramedullary Disease in B cell ALL

Adult B cell ALL subjects with known extramedullary disease at baseline will be assessed with imaging within 28 days prior to administration of CTX110, and postinfusion imaging will be conducted per the schedule of assessments in Table 16 and Table 17. A modality appropriate for the anatomical location of disease will be used with the same imaging modality for the duration of participation. Extramedullary disease will be assessed as described in Appendix F .

7.2.16. Bone Marrow Biopsy and Aspirate for NHL

A bone marrow biopsy and aspirate will be performed at screening (or within 28 days prior to CTX110 infusion, if a recent sample was collected as part of standard of care) and at Day 28 to evaluate extent of disease. A bone marrow biopsy at Day 28 is required for NHL subjects with BM involvement at screening. Subjects with history of bone marrow involvement who achieve a CR as determined on PET/CT scan will have a bone marrow biopsy to confirm response assessment. If a subject shows signs of relapse, the biopsy collection should be repeated. A sample of aspirate for presence of CTX110 (detected via PCR) should be sent for central laboratory evaluation at any point when bone marrow analysis is performed. Standard institutional guidelines for the bone marrow biopsy should be followed. Further instructions on processing and shipment are provided in the Laboratory Manual. [redacted]

7.2.17. Optional Tumor Biopsy for NHL

To understand more about the trafficking of CTX110 into the tumor tissue and the impact of tumor environment on the function of CTX110, optional tumor biopsies will be obtained from subjects with tumor amenable to biopsy and who provide separate consent for this procedure. The optional tumor biopsy will be performed at Day 28. Standard institutional guidelines for the

tumor biopsy should be followed. Further instructions on processing and shipment are provided in the Laboratory Manual.

7.2.18. Bone Marrow Biopsy and Aspirate for B Cell ALL

A bone marrow biopsy and aspirate will be performed during the screening window or within 28 days of CTX110 infusion with appropriate consent. Samples will be assessed locally to confirm disease pathology, evaluate extent of disease, and assign cohorts. Samples will also be assessed (locally and centrally) for MRD by multicolor flow cytometry or molecular approaches (e.g., PCR, NGS). Subjects in Subcohort D2 may be enrolled with local baseline MRD results pending, as long as qualifying results within 3 months of enrollment are available.

Additional bone marrow aspirates and biopsy will be performed at subsequent visits per the schedule of assessments in Table 16. If a subject shows signs of relapse, the biopsy and aspirate collection should be repeated. Disease assessments will be performed according to criteria in Appendix F. A sample for presence of CTX110 (detected via PCR) should be sent for central laboratory evaluation at any point when bone marrow analysis is performed.

Standard institutional guidelines for bone marrow biopsy and aspirate collection should be followed. Further instructions on processing and shipment are provided in the Laboratory Manual. [redacted]

7.2.19. Laboratory Tests

Laboratory samples will be collected and analyzed according to the schedule of assessment in Table 16, Table 17, and Table 18. Local laboratories meeting Clinical Laboratory Improvement Amendments requirements will be utilized to analyze all tests listed in Table 19 according to standard institutional procedures.

Table 19: Local Laboratory Tests

Hematology	Hematocrit, hemoglobin, red blood cell count, white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils, platelet count, absolute neutrophil count, ABO type,[1] [redacted] peripheral blasts in Cohort D
[redacted]	
Serum Chemistry	ALT (SGPT), AST (SGOT), total bilirubin, albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, eGFR, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, CRP, ferritin
Coagulation	Prothrombin time, activated partial thromboplastin time, international normalized ratio, fibrinogen
Infectious Disease	HIV-1, HIV-2, hepatitis C virus antibody and PCR, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody
Immunological[2]	CD19, CD20, IgA, IgG, IgM
Serum or Urine Pregnancy[3]	Human chorionic gonadotropin

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CD: cluster of differentiation; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HIV-1/-2: human immunodeficiency virus type 1 or 2; HLH: hemophagocytic lymphohistiocytosis; IgA/G/M: immunoglobulin A, G, or M; LD: lymphodepleting; PCR: polymerase chain reaction; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; [redacted]

[1.] For Cohort C only, if necessary.

[2.] CD19 and CD20 should be evaluated in the same assay to detect CD19 antigen loss.

[3.] For females of childbearing potential only. Serum pregnancy test required at screening. Serum or urine pregnancy test within 72 hours of start of LD chemotherapy (Phase 1 Cohorts A, B, and D and Phase 2) or daratumumab (Phase 1 Cohort C) or additional infusion of CTX110, if applicable, when administered without daratumumab or LD chemotherapy. See Section 7.2.5 for additional details.

7.3. Biomarkers

Blood, bone marrow, tumor, and CSF samples (only in subjects with ICANS) will be collected to [redacted]

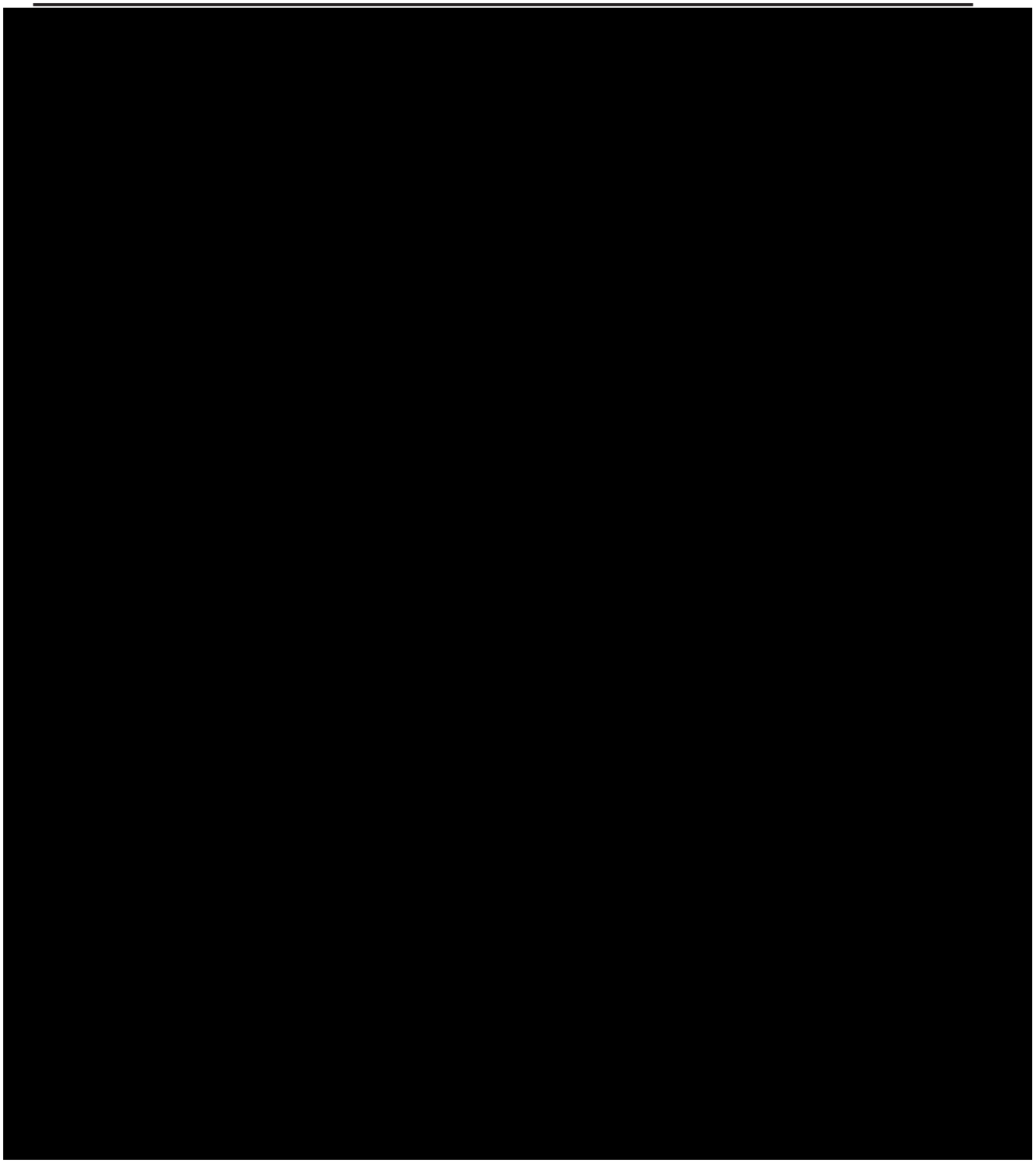
The following labs will be drawn for analysis at a central laboratory. Reference the Laboratory Manual for information regarding the blood draw and sample handling for tests sent to the central laboratory for processing. [redacted]

7.3.1. CTX110 Pharmacokinetic Analysis

PK analysis of CTX110 cells will be performed on blood samples collected according to the schedule described in Table 16, Table 17, and Table 18. In subjects experiencing signs or symptoms of CRS, neurotoxicity, and HLH, additional blood samples should be drawn in intervals outlined in the laboratory manual. The time course of the disposition of CTX110 in blood (Tsai et al., 2017) will be described using a PCR assay that measures copies of CAR construct per µg DNA. Complementary analyses using flow cytometry to confirm the presence of CAR protein on the cellular surface may also be performed.

The trafficking of CTX110 in CSF, bone marrow, or tumor tissues may be evaluated in any of these samples collected as per protocol-specific sampling.

[redacted]



8. SAFETY, ADVERSE EVENTS, AND STUDY OVERSIGHT

The investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigator will assess and record details, including the date of onset, event diagnosis (when known) or signs and symptoms, time course (end date, ongoing, intermittent), relationship to the study therapies or procedure, action(s) taken, and outcome. AEs in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. The investigator is responsible for ensuring that any AEs observed by the Investigator or reported by the subject are recorded in the subject's medical record in the sponsor's electronic data capture system.

8.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not considered related to the medicinal (investigational) product [(GCP) E6(R2)]. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

The investigator will assess and record information pertaining to the AE, which includes but is not limited to the following: date of onset, event diagnosis (when known) and/or signs and symptoms, duration, severity, seriousness, relationship to the study therapy or procedure, action(s) taken, and outcome.

Additional criteria defining an AE are described below.

The following **are** considered to be AEs:

- Aggravation of a pre-existing disease or permanent disorder (any clinically significant worsening in the nature, severity, frequency, or duration of a pre-existing condition)
- Events resulting from protocol-mandated procedures (e.g., complications from invasive procedures)

The following **are not** considered to be AEs:

- Medical or surgical procedures including elective or preplanned procedures such as surgery, endoscopy, tooth extraction, and transfusion. These should be recorded in the relevant eCRF.
  - Note: An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.
- Pre-existing diseases or conditions that do not worsen during or after administration of the investigational medicinal product
- Hospitalization planned for study treatment infusion or observation

- The malignancy under study or signs and symptoms associated with the disease (except signs and symptoms of disease progression that meet seriousness criteria within 3 months after CTX110 administration) as well as progression or relapse of the underlying malignancy (see Section 8.10 disease progression)

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline value. Only abnormal laboratory results considered by the investigator to be clinically significant should be reported as AEs (e.g., an abnormal laboratory finding associated with clinical symptoms, of prolonged duration, or that requires additional monitoring and/or medical intervention). Whenever possible, these should be reported as a clinical diagnosis rather than the abnormal parameter itself (i.e., neutropenia vs neutrophil count decreased). Abnormal laboratory results without clinical significance should not be recorded as AEs.

Adverse events can occur before, during, or after treatment, and can be either treatment-emergent (AEs that start or worsen on or after CTX110 infusion) or non–treatment-emergent. A non–treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that occurs after written informed consent has been obtained and before the subject has received CTX110.

8.2. Serious Adverse Event

An AE of any untoward medical consequence must be classified as an SAE if it meets any of the following criteria:

- Results in death
- Is life-threatening (i.e., an AE that, in the opinion of the investigator, places the subject at immediate risk of death)
- Requires in-patient hospitalization or prolongs an existing hospitalization (hospitalizations for scheduled medical or surgical procedures or to conduct scheduled treatments do not meet these criteria)
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect in the newborn
- Other important/significant medical events. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalization for study treatment infusions, or planned hospitalizations following CTX110 infusion, are not considered SAEs. Furthermore, hospitalizations for observation or prolongation of hospitalization for observation alone should not be reported as an SAE unless they are associated with a medically significant event that meets other SAE criteria as assessed by the investigator.

8.3. Adverse Events of Special Interest

An AESI, whether serious or nonserious, is one of scientific and medical concern specific to the sponsor's product or program for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate.

Based on the reported clinical experience of autologous CAR T cells, considered to be in the same pharmacological class, the sponsor has identified the following AESIs:

- CTX110 infusion reactions
- Grade ≥ 3 infections
- Tumor lysis syndrome
- Cytokine release syndrome
- ICANS
- B cell aplasia
- Hemophagocytic lymphohistiocytosis
- Hypogammaglobulinemia
- Graft vs host disease
- Secondary malignancy
- Uncontrolled T cell proliferation
- Any new hematological or autoimmune disorder that the investigator determines is possibly related or related to CTX110.

Additional information on the required AESI reporting collection period is detailed in Table 21.

8.4. Adverse Event Severity

The investigator is obligated to grade AEs according to CTCAE version 5.0 (Appendix E), with the exception of CRS, neurotoxicity, and GvHD, which will be graded according to the criteria in Section 6.2.4, Section 6.2.5, and Section 6.2.9, respectively.

When a CTCAE grade or protocol-specified criteria are not available, the investigator will use the toxicity grading in Table 20.

Table 20: Adverse Event Severity

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[1]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[2]

Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

ADL: Activities of Daily Living; AE: adverse event.
[1.] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2.] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.5. Adverse Event Causality

The investigator must assess the relationship between each AE and CTX110, LD chemotherapy, daratumumab infusion, and any protocol-mandated study procedure (all assessed individually). The assessment of relationship will be made based on the following definitions:

Related: There is a clear causal relationship between the study treatment or procedure and the AE.

Possibly related: There is some evidence to suggest a causal relationship between the study treatment or procedure and the AE, but alternative potential causes also exist.

Not related: There is no evidence to suggest a causal relationship between the study treatment or procedure and the AE.

Investigators should consider the temporal association between the timing of the event and administration of the treatment or procedure, a plausible biological mechanism, and other potential causes of the event (e.g., concomitant therapy, underlying disease) when making their assessment of causality.

If an SAE is assessed to be not related to any study intervention, an alternative etiology must be provided in the CRF.

If the relationship between the SAE and the investigational product is determined to be "possible," a rationale for the assessment must be provided by the reporting investigator.

8.6. Outcome

The outcome of an AE or SAE classified and reported as follows:

- Fatal
- Not recovered/not resolved
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Unknown

8.7. Adverse Event Collection Period

The safety-related information of all subjects enrolled in this study will be recorded from the time of ICF signing until end of study; however, there are different reporting requirements for the different time periods in the study. Table 21 describes the AEs that should be reported at each time period of the study.

Table 21: Adverse Event Collection by Study Time Period

Time Period	AE Reporting Requirements
Informed consent to 3 months after each CTX110 infusion[1]	• All AEs[2]
3 months after last CTX110 infusion through Month 24 visit	• Nonserious AEs related to LD chemotherapy, study procedure,[3] or CTX110 • SAEs • AESIs
Month 24 to Month 60 visit OR any time a subject starts a new [redacted]	• SAEs related to LD chemotherapy, study procedure,[3] or CTX110 • AESIs related to LD chemotherapy, study procedure,[3] or CTX110 • New malignancies

AE: adverse event; AESI: adverse event of special interest; LD: lymphodepleting; SAE: serious adverse event.
1. If additional infusion of CTX110 occurs after the 3-month post-CTX110 infusion period, then the AE reporting for any additional CTX110 infusion begins with daratumumab or LD chemotherapy administration, as applicable.
2. SAEs related to disease progression, including SAEs related to disease progression with outcome of death, will be reported up to 3 months. SAEs related to disease progression will not be collected after 3 months. Deaths due to disease progression after 3 months must be reported as outlined Section 8.11 .
3. AEs related to study procedure include events related to, e.g., laboratory procedures, radiography, biopsies, bone marrow aspirates, or IV treatment infusions, and may occur at any time starting at screening and continuing through the duration of the study.

If a subject does not receive CTX110 therapy after enrollment, the AE reporting period ends 30 days after last study-related treatment or procedure (e.g., biopsy, imaging, LD chemotherapy).

8.8. Adverse Event Reporting

All AEs will be recorded in the appropriate section of the electronic case report form (eCRF). Subjects withdrawn from the study because of AEs will be followed by the investigator until the outcome is determined. When appropriate, additional written reports and documentation will be provided.

AE reporting should occur as per the study period designated in Table 21. If a reportable SAE or AESI occurs, the **SAE/AESI form** provided to investigators should be completed and submitted to the sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) by scanning and emailing the paper report form using the email address provided to the investigators. In particular, if the SAE is fatal or life-threatening, the report form must be submitted immediately, irrespective of the extent of available AE information. The time frame also applies to additional, new information (follow-up) on previously reported SAE/AESI reports.

In the rare event that the investigator does not become aware of the occurrence of a reportable SAE/AESI immediately (e.g., a study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours of learning of the event and document the date and time of awareness of the event.

In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion (e.g., autopsy finding). The information collected for SAEs/AESIs is more detailed than that captured on the AE CRF. In general, this will include a description of the event in sufficient detail, as well as concomitant medications and any relevant medical details to allow for a complete medical assessment of the case and causality assessment by the investigator and the sponsor. Information on the other possible causes of the event, such as concomitant medications and illnesses must be provided.

The investigator must complete, sign, and date the SAE/AESI form, verify the accuracy of the information recorded on the SAE/AESI form with the corresponding source documents, and send a copy by email or fax to the sponsor or designee. Subsequently, all SAEs will be reported to the health authorities per local reporting guidelines.

It is the principal investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site as per local policies. Investigators will also be notified of all unexpected, serious, drug-related events that occur during the clinical trial. Each site is responsible for notifying its IRB/EC of these additional SAEs.

8.9. Pregnancy

Certain information, although not considered an AE or SAE, must be recorded, reported, and followed as indicated for an SAE (see Section 8.8), including pregnancies.

Pregnancies (both those of female subjects and female partners of male subjects) must be reported to the sponsor or designee within 24 hours of the investigator's knowledge using the Investigational Product Pregnancy Report. All pregnancies will be followed through to outcome and the outcome must be reported to the sponsor or designee using the Pregnancy outcome section of Investigational Product Pregnancy Report.

Pregnancies themselves are not considered AEs or SAEs. However, any AEs or SAEs occurring during pregnancy are to be reported following AE and SAE reporting guidelines.

8.10. Disease Progression

Progression of malignancy is not considered an adverse event, and the term "disease progression" or similar should not be reported as an AE. However, within 3 months after CTX110 administration, signs and symptoms of disease progression meeting seriousness criteria should be reported as SAEs (including SAEs with the outcome of death), as per Table 21. Whenever possible, the event should be reported as a clinical diagnosis (e.g., respiratory failure or pulmonary hemorrhage). For reporting of disease progression with outcome of death ≥3 months after CTX110 administration, refer to Section 8.11.

8.11. Reporting Deaths

Regardless of relationship to study drug, all deaths on study should be recorded in the relevant eCRF.

- In addition, all outcomes of death must be reported to the sponsor according to the AE collection periods described in Section 8.7 and according to the information provided in Section 8.8.
- For any death that does not meet reporting criteria in Section 8.7, the death must be reported on the **Death Report Form**. An example of a situation where the Death Report Form should be used would be a death due to disease progression that occurs more than 90 days after CTX110 infusion.

8.12. Study Oversight

8.12.1. Safety Review Committee

During dose escalation, an SRC composed of Part A investigators and sponsor representatives will meet before each dose escalation decision and before initiating a new dose cohort. The SRC will review and discuss all AEs and determine if they meet DLT criteria and/or study stopping rules (Section 4.1.4.2 and Section 9). After 3 or 6 subjects are enrolled in a dose level, the SRC will review aggregate safety data and decide whether to dose escalate, de-escalate, or confirm the recommended Part B dose according to the rules in Section 4.1.4. The SRC may consult with the DSMB via the sponsor regarding emergent safety data and discuss potential revisions to DLT criteria or alternate dosing schema.

In Part B, the SRC may continue to meet regularly to discuss one or more of the following: single subject case studies, aggregate safety and/or biomarker data, toxicity management algorithms, and review and discuss the possibility of expanding the study to include other malignancies.

8.12.2. Independent Data Safety Monitoring Board

An independent DSMB comprised of at least 2 physicians and 1 statistician with appropriate scientific and medical expertise to monitor the study will be established during Part A. The DSMB will perform interim analyses of safety and efficacy data according to Section 10.5 and will monitor stopping rules to pause enrollment. The DSMB will also review expedited reports of any SAEs, including expedited SAEs or SAEs resulting in death. The DSMB may recommend that the sponsor amend the protocol, stop enrollment, or discontinue the study at any time if concerns about safety of the subjects are encountered. The roles and responsibilities of the DSMB will be further described in the DSMB charter.

9. STOPPING RULES AND STUDY TERMINATION

9.1. Stopping Rules

A Phase 1 cohort will be paused if one or more of the following events occur:

- Life-threatening (grade 4) toxicity attributable to CTX110 that is unmanageable, unexpected, and unrelated to LD chemotherapy
- Death related to CTX110 within 30 days of infusion
- Grade 3 or higher GvHD
- After at least 12 subjects are enrolled in cohort expansion and at least 1 of the following occurs:
  - >35% grade 3 or 4 neurotoxicity not resolving within 2 weeks to grade ≤2
  - >20% grade ≥2 GvHD that is steroid refractory.
  - >30% grade 4 CRS
- New malignancy (distinct from recurrence/progression of previously treated malignancy)
- Lack of efficacy, defined as 2 or fewer objective responses (per central review) after 15 subjects in cohort expansion (Phase 1 Part B) have 3 months of post-CTX110 assessment.

If there is any such event(s), enrollment will be suspended, all available data will be reviewed, and health authorities will be notified as required. A meeting will take place with the SRC, members of the study team, and sponsor medical monitor. Meeting minutes will be taken to capture the review of any ongoing investigations, including next steps in management of the subject and any proposed changes to the protocol for forwarding to the DSMB. After evaluation and following a review of the data with the DSMB, the sponsor may decide to restart enrollment in a cohort, amend the study, or permanently suspend enrollment and remove all subjects who have not received CTX110 from the study. Discontinuation or suspension of enrollment in one particular disease subset or cohort may not be applicable to others.

For Phase 2, the DSMB will review available safety data on at least a semi-annual basis and make trial conduct recommendations based on analysis of the risk-benefit balance. The DSMB may request additional safety data or may recommend modifying the study conduct if safety concerns are identified. The DSMB will also review safety data in parallel to the interim analysis for futility and efficacy (Section 10.5.1). The overall study will be paused if the sponsor or health authorities decide for any reason that patient safety may be compromised by continuing the study.

In the event enrollment is permanently suspended, subjects who are already enrolled in the study will not proceed with daratumumab infusion (Phase 1 Cohort C), LD chemotherapy (all Phase 1 cohorts and Phase 2), and CTX110 infusion (all Phase 1 cohorts and Phase 2). Subjects who have already been treated with CTX110 will remain in the study and continue to be followed per the study protocol or will be transitioned to a long-term safety follow-up study.

If enrollment is suspended after a subject (or subjects) has received daratumumab (Cohort C) or LD chemotherapy before they have received CTX110 (all cohorts), the decision to infuse CTX110 will be at the investigator's discretion after discussion of the potential risks with the subject. The investigator should inform the CRISPR medical monitor of the decision before infusion of CTX110.

If enrollment is permanently suspended, the sponsor will immediately inform all appropriate parties, including principal investigators, ECs, IRBs, and competent authorities.

9.2. Stopping Rules for Individual Subjects

Stopping rules for individual subjects are as follows:

- Any medical condition that, in the opinion of the investigator, would put the subject at risk during continuing study-related treatments or follow-up
- If a subject is found not to have met eligibility criteria or has a major protocol deviation before the start of LD chemotherapy (Cohorts A, B, D), or before the start of daratumumab infusion (Cohort C)
- If a subject has unresolved infusion reaction due to daratumumab treatment (Cohort C)

9.3. End of Study Definition

The end of the study is defined as the time at which the last subject completes the Month 60 visit, is considered lost to follow-up, withdraws consent, or dies. The primary analyses of Phase 2 will be conducted after the 97 subjects have completed the 6-month disease response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first.

9.4. Study Termination

This study may be discontinued at any time due to safety concerns, failure to meet expected enrollment goals, administrative reasons, or at the discretion of the sponsor. In the event of study termination, the sponsor will immediately inform all appropriate parties, including principal investigators, ECs, IRBs, and competent authorities. In the event this study is terminated early, subjects who have received CTX110 will be asked to participate in a separate long-term follow-up study for up to 15 years after the last CTX110 infusion.

9.5. Long-Term Follow-up Study

The long-term follow-up study is a separate, noninterventional safety study. Subjects in the current study (CRSP-ONC-001) will be asked to consent to be followed for safety for up to 15 years from their last CTX110 infusion. Subjects may be rolled over into the long-term follow-up study once they have entered secondary follow-up in CRSP-ONC-001, if the long-term follow-up study has been approved at the investigative site. Details regarding the long-term follow-up study requirements will be specified in a separate protocol.

10. STATISTICAL ANALYSES

10.1. Study Objectives and Hypotheses

Phase 1

The primary objective of Part A is to assess the safety of escalating doses of CTX110 in combination with various lymphodepletion agents in subjects with relapsed or refractory B cell malignancies to determine the recommended Part B dose and cohort.

The primary objective of Part B is to assess the preliminary efficacy of CTX110 in subjects with relapsed or refractory B cell malignancies, as measured by ORR.

Phase 2

The primary objective of Phase 2 is to assess the efficacy of CTX110 in subjects with select NHL subtypes, as measured by ORR.

10.2. Study Endpoints

10.2.1. Primary Endpoints

Phase 1

Part A (dose escalation) for all cohorts: The incidence of AEs, defined as DLTs for each of the cohorts (A, B, C, and D).

Part B (cohort expansion) and Phase 2: The ORR (CR + PR) per the Lugano Response Criteria for Malignant Lymphoma (Cheson et al., 2014), as determined by independent central review.

10.2.2. Secondary Efficacy Endpoints (Phase 1 and Phase 2)

Duration of response/remission (DOR) based on central read/assessment will be reported only for subjects who have had objective response events. This will be assessed using the time between the first objective response and the first disease progression or death due to any cause after the first objective response.

Duration of clinical benefit (DOCB) based on central read/assessment will be calculated as the time between the first objective response and the last disease progression or death.

Treatment-failure–free survival (TFFS) will be calculated as the time between the first CTX110 infusion and the last disease progression or death due to any cause.

Progression-free survival (PFS) will be calculated as the time between the first CTX110 infusion and the first disease progression or death due to any cause.

Overall survival (OS) will be calculated as the time between date of first CTX110 infusion and death due to any cause.

For secondary efficacy endpoints DOR, DOCB, TFFS and PFS, the subjects who have not progressed and are still on study at the data cutoff date will be censored at their last response

assessment date. For OS, the subjects who are alive at the data cutoff date will be censored at their last date known to be alive.

For adult B cell ALL (Phase 1 Cohort D), ORR (complete remission + CRi) will be assessed.

10.2.3. Secondary Safety Endpoints (Phase 1 and Phase 2)

The frequency and severity of AEs and clinically significant laboratory abnormalities will be summarized and reported according to CTCAE version 5.0, except for CRS (ASTCT criteria, Section 6.2.4), neurotoxicity (ICANS, Section 6.2.5, and CTCAE v5.0), and GvHD (Mount Sinai Acute GVHD International Consortium [MAGIC] criteria, Section 6.2.9).

10.2.4. Pharmacokinetics (Phase 1 and Phase 2)

Pharmacokinetic data will include levels of CTX110 in blood over time as assessed by a PCR assay that measures copies of CAR construct. Analysis of CTX110 in blood may also occur using flow cytometry that detects CAR protein on the cellular surface. Such analysis may be used to confirm the presence of CTX110 in blood and to further characterize other cellular immunophenotypes.

10.2.5. Secondary Patient-reported Outcome Endpoint (Phase 1 and Phase 2)

Change over time in PROs associated with CTX110 will be evaluated and analyzed as in Section 10.6.5. See Section 7.2.13 for the PRO surveys administered to subjects in various cohorts.

10.3. Analysis Sets

The following analysis sets will be evaluated and used for presentation of the data.

Phase 1 Part A (Dose Escalation)

DLT evaluable set (DES): All subjects who receive CTX110 and complete the DLT evaluation period or discontinue early after experiencing a DLT. The DLT evaluation period will begin with first CTX110 infusion and last for 28 days. The DES will be used for determination of the recommended Part B or Phase 2 dose.

Phase 1 Part A and Part B (Dose Escalation and Cohort Expansion) and Phase 2

Enrolled set: All subjects enrolled in the study. The enrolled set will be classified according to the assigned dose level of CTX110.

Treated set: All subjects who received any study treatment in the study. The subjects in the treated set will be classified according to the received study treatment.

Full analysis set (FAS): All subjects who received CTX110 infusion. The subjects in FAS will be classified according to the assigned dose regimen of CTX110. Only subjects in the FAS who are assigned to the dose regimen for Phase 2 will be used for the primary efficacy analysis.

Safety analysis set (SAS): All subjects who received CTX110 infusion. The subjects in SAS will be classified according to the received dose level of CTX110. The SAS will be the primary analysis set for the characterization of CTX110 safety profile.

10.4. Sample Size

The sample size in Phase 1 Part A (dose escalation) of the study will be approximately 100, i.e., approximately 70 subjects with NHL and approximately 30 subjects with B cell ALL, depending on the number of dose levels and cohorts evaluated, and the occurrence of DLTs. The sample size in Phase 1 Part B (cohort expansion) will be up to 30.

To test for efficacy, group sequential design with alpha-spending function (Lan and DeMets, 1983) will be employed. One interim analysis is planned for both futility and early efficacy. It will be performed at an information level of 0.5 (proportion of total subjects), and boundaries based on error-spending function will be used for the interim analysis.

[redacted]

[redacted]

10.5. Interim Analyses

10.5.1. Efficacy Interim Analysis

[redacted]

10.5.2. Safety Interim Analyses

The DSMB will review safety data from dose escalation (Phase 1 Part A) and endorse the recommended Part B or Part 2 dose before the study advances to cohort expansion or Phase 2. The DSMB will review safety data twice a year until the last treated subject in Part B or Phase 2 is at least 2 years after last CTX110 infusion. The sponsor or SRC may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate timely DSMB review.

10.6. Planned Method of Analyses

The primary analysis of efficacy will occur after all subjects in the FAS in Phase 2 of the study have had the opportunity to be assessed for response 6 months after CTX110 infusion. A final analysis will occur when all subjects complete or withdraw from the study.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. By-subject listings will be provided for all data, unless otherwise specified.

10.6.1. Efficacy Analysis

The primary endpoint of ORR for all analyses (interim and primary) will be based on independent central review of disease assessments in the FAS.

Sensitivity analyses of ORR based on investigator review of disease assessments will be performed. For NHL, Lugano response criteria (Cheson et al., 2014) will be used and ORR refers to the rate of CR + PR (Appendix A). For B cell ALL, ORR refers to the rate of complete remission + CRi (Appendix F).

Objective response rate will be summarized as a proportion with exact 95% confidence intervals.

For time-to-event variables such as DOR, DOCB, TFFS, PFS, and overall survival, medians with 95% confidence intervals will be calculated using Kaplan-Meier methods.

10.6.2. Safety Analysis

All subjects who receive CTX110 will be included in the safety analysis set. Clinical AEs will be graded according to CTCAE version 5.0, except for CRS, which will be graded according to ASTCT (Lee et al., 2019), neurotoxicity, which will be graded according to ICANS (Lee et al., 2019) and CTCAE, and GvHD, which will be graded according to MAGIC criteria (Harris et al., 2016). AEs, SAEs, and AESIs will be summarized and reported according to the collection by study time period described in Table 21.

Treatment-emergent adverse events are defined as AEs that start or worsen on or after the initial CTX110 infusion.

Vital signs will be listed. Summary tables will be prepared to examine the distribution of laboratory measures over time.

Frequencies of subjects experiencing at least 1 AE will be reported by body system and preferred term according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. Detailed information collected for each AE will include description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, clinical outcome, and whether or not it was a DLT. Emphasis in the analysis will be placed on AEs classified as dose-limiting.

10.6.3. Pharmacokinetic and Pharmacodynamic Analyses

Incidence of [redacted] levels of CTX110 CAR$^+$ T cells in blood, and levels of [redacted] in serum will be summarized.

[redacted]

[redacted]

10.6.5. Patient-reported Outcomes

Descriptive statistics will be presented for PRO, both as reported and as change from baseline. Further analyses may be performed on an ad hoc basis.

11. DATA MANAGEMENT

11.1. Data Recording and eCRF Processing

The investigator is required to maintain adequate and accurate medical records designed to record all observations and data pertinent to the study for each subject. Study data for each consented subject will be entered into a CRF by site personnel using a secure, validated (21 CFR Part 11 compliant), web-based electronic data capture application. Instances of missing, discrepant, or uninterpretable data will be queried by the sponsor or designee for resolution. Any changes to study data will be made to the eCRF and documented in an audit trail maintained within the clinical database. CRFs must be reviewed and electronically signed and dated by the investigator.

An audit may be performed at any time during or after completion of the clinical study by sponsor personnel or their designee. All study-related documentation must be made available to the designated auditor.

12. ADMINISTRATIVE

12.1. Institutional Review Board/Ethics Committee

This protocol and the proposed ICF must be reviewed and approved by the appropriate IRB/EC prior to the start of the study. During the study, the investigator shall make timely and accurate reports to the IRB/EC on the progress of the trial, at intervals not exceeding 1 year, as well as satisfying any other local IRB/EC regulations regarding reporting. Copies of all reports to and correspondence with and from the IRB/EC must be provided to the sponsor or its designee.

Any significant changes or revisions in the study protocol or any changes that may alter subject risk must be approved in writing by the IRB/EC prior to implementation. A protocol change intended to eliminate an apparent immediate hazard may be implemented immediately provided that the sponsor is immediately notified, and an amendment is subsequently provided by the sponsor and approved by the IRB/EC.

It is the investigator's obligation to maintain an IRB/EC correspondence file, and to make this available for review by sponsor representatives or their designee as part of the study monitoring process.

12.2. Study Conduct

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

12.3. Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all data provided to the sponsor or designee, study reports, and communications relating to the study will identify subjects by assigned subject numbers, and access to subject names linked to such numbers shall be limited to the site and the study physician and shall not be disclosed to the sponsor or designee. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow the sponsor and/or its representatives access to all pertinent medical records to allow for the verification of data gathered and the review of the data collection process. The regulatory authorities in other jurisdictions, including the IRB/EC, may also request access to all study records, including source documentation, for inspection.

12.4. Written Informed Consent

The investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific screening and entry into the study. A copy of the signed document will be provided to the subject, and a copy will be maintained with the subject's records. The original will be retained by the investigator. The source documents for each subject shall document that the informed consent was obtained prior to participation in the study.

The investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects

must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated ICF must be obtained before conducting any study procedures. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject. Whenever important new information becomes available that may be relevant to the subject's consent, the written ICF and any other written information provided to subjects will be revised by the sponsor or designee and be submitted again to the IRB/EC for review and favorable opinion. The agreed upon, revised information will be provided to each subject in the study for signing and dating. The investigator will explain the changes to the previous version.

12.5. Delegation of Investigator Responsibilities

The investigator will ensure that all persons involved in the conduct of the study are informed about the protocol, protocol amendments, study procedures, and study-related duties.

12.6. Study Files

Documentation concerning investigators' credentials and experience, and IRB approval of protocol and ICF, and other documentation are required prior to shipment of study drug to the study site. Copies of these documents as well as supplemental information, such as the Investigator's Brochure, will be kept onsite in an investigator study file binder. This file also will contain drug accountability (receipt/dispensing) records, sponsor/investigator correspondence, IRB correspondence, changes to the protocol, information regarding monitoring activities, subject exclusion records, and biological sample records.

12.7. Retention of Study Documents

All study documents, including records of drug receipt and disposition, copies of eCRFs, as well as supporting documentation and administrative records, must be retained by the investigator for a minimum of 2 years following notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved. No study documents will be destroyed or moved to a new location without prior written approval from the sponsor. If the investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed upon designee, such as the study monitor, another investigator, or the institution where the study was conducted. The sponsor should be notified in writing at least 30 days prior to the disposal of any study records related to this protocol.

12.8. Protocol Compliance

No modifications to the protocol will be made without the approval of both the investigator and the sponsor. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (e.g., efficacy assessments) will require IRB/EC notification before implementation, except where the modification is necessary to

eliminate an apparent immediate hazard to human subjects. The sponsor will submit all protocol modifications to the required regulatory authorities.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed crucial for the safety and well-being of that subject may be instituted for that subject only. The investigator or other attending physician also will contact the sponsor as soon as possible in the case of such a departure. These departures do not require preapproval by the IRB; however, the IRB and sponsor must be notified in writing as soon as possible after the departure has been made. In addition, the investigator will document the reasons for protocol deviation and the ensuing events.

12.9. Monitoring Functions and Responsibility

Before an investigational site can enter a subject into the study, a representative of CRISPR will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of CRISPR or its representatives. This will be documented in a Clinical Study Agreement between CRISPR and the investigator.

During the study, a monitor from CRISPR or representative will have regular contacts with the investigational site to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to CRISPR
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to CRISPR and those SAEs that met criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

12.10. Quality Control and Quality Assurance

Authorized representatives of CRISPR, a regulatory authority, an EC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a

CRISPR audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported per the protocol, ICH/GCP guidelines, and any applicable regulatory requirements. The investigator should contact CRISPR immediately if contacted by a regulatory agency about an inspection.

12.11. Disclosure of Data

All information obtained during the conduct of this study will be regarded as confidential. Disclosures (i.e., any release of information to any third party not noted herein) of any, not previously known to be public, information and/or results of the investigation for publication or by capsules or poster presentation shall not be made earlier than 30 days after submission of the proposed material to the sponsor for inspection, unless the sponsor consents to earlier disclosure. The investigator will take appropriate cognizance of the sponsor's suggestions before disclosure for publication or presentation consistent with protection of the sponsor's right to its confidential data.

12.12. Confidentiality and Publication

All scientific, commercial, and technical information disclosed by CRISPR in this protocol or elsewhere will be considered the confidential and proprietary property of CRISPR. The investigator will hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator will not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by CRISPR in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide CRISPR with complete test results and all data developed in the study.

Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;
3. Final approval of the version to be published; and

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

An individual must meet all criteria to be an author on any publication containing data from this study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between CRISPR and the investigator and/or the investigator's institution.

12.13. Clinical Study Report

After completion of the study, a clinical study report, written by the sponsor or designee in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

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14. APPENDICES

14.1. Appendix A: Lugano Response Evaluation Criteria in Lymphoma

The Lugano Classification (Cheson et al., 2014) provides a standardized way to assess imaging in lymphoma subjects. It is comprised of radiologic assessments of tumor burden on diagnostic CT, and metabolic assessments on F^{18} FDG-PET for FDG-avid histologies.

Table 23: Lugano Classification Assessment Components

<table>
<tr><th>Diagnostic CT/MRI</th><th>F^{18} FDG-PET</th></tr>
<tr><td>Target Lymph Nodes and Extra Nodal Lesions
Up to 6 of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the subject's overall disease burden and include mediastinal and retroperitoneal disease, if involved.
• Nodal disease: Must have an LDi >1.5 cm
• Extranodal disease: Must have an LDi >1.0 cm
Non-Measured Lesions
All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).
Organ Enlargement (Spleen)
The spleen is considered enlarged (splenomegaly) when >13 cm in the cranial to caudal dimension.
New Lesions
• Nodal disease: Must have an LDi >1.5 cm
• Extranodal disease: Any size</td><td>5 Point Scale (Deauville) PET Score (Lymph Nodes and Extra Lymphatic Sites)[1]
The 5-point scale scores the site of the most intense FDG uptake for the time point, as follows:
<table><tr><th>Score</th><th>Criteria</th></tr><tr><td>1</td><td>No uptake</td></tr><tr><td>2</td><td>Uptake ≤ mediastinum</td></tr><tr><td>3</td><td>Uptake > mediastinum but ≤ liver</td></tr><tr><td>4</td><td>Uptake moderately higher than liver (moderately indicates uptake greater than normal liver)</td></tr><tr><td>5</td><td>Uptake markedly higher than liver (markedly indicates much higher than normal liver)
and/or
New lesions</td></tr><tr><td>X</td><td>New areas of uptake unlikely to be related to lymphoma</td></tr></table>Bone Marrow: FDG uptake assessed as
• No FDG uptake consistent with lymphoma
• Focal FDG uptake consistent with lymphoma
• Diffuse FDG uptake consistent with lymphoma</td></tr>
</table>

CT: computed tomography; F^{18} FDG: fluorodeoxyglucose F18; LDi: longest diameter; MRI: magnetic resonance imaging; PET: positron emission tomography.
[1.] See (Barrington et al., 2014)

Table 24: Lugano Criteria for Response Assessment

At each follow-up time point, a PET-based response and a CT-based response will be made per the definitions below.

Response and Site	PET-based Response	CT-based Response
COMPLETE		
	Complete Metabolic Response[1] **ALL of the following**	**Complete Radiologic Response ALL of the following**
Lymph nodes, extranodal lesions	Score of 1, 2, or 3[1]	• Lymph nodes: All <1.5 cm in longest diameter. • Extralymphatic disease absent.
Nonmeasured lesion	N/A	Absent
Organ enlargement	N/A	Spleen: normal size
New lesions	No new metabolically active lesions (new lesions drive score 5)	None
Bone marrow	No FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative.
PARTIAL		
	Partial Metabolic Response	**Partial Remission ALL of the following**
Lymph nodes, extranodal lesions	Score of 4, or 5 with reduced uptake from baseline and residual masses of any size	≥50% decrease in SPD of all target lesions from baseline
Nonmeasured lesion	N/A	Absent, normal, or regressed, but no increase
Organ enlargement	N/A	Spleen: ≥50% decrease from baseline in enlarged portion
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (e.g., persistent focal changes in the marrow with nodal response)	N/A
NO RESPONSE/STABLE DISEASE		
	No Metabolic Response	**Stable Disease**
Lymph nodes, extranodal lesions	Score of 4, or 5 with no significant change in FDG uptake from baseline	• <50% decrease in SPD of all target lesion from baseline • No progression
Nonmeasured lesion	N/A	No increase consistent with progression
Organ enlargement	N/A	Spleen: No increase consistent with progression
New lesions	None	None

Response and Site	PET-based Response	CT-based Response
Bone marrow	No change from baseline	N/A
PROGRESSION		
	Progressive Metabolic Response	**Progressive Disease** **ANY of the following**

Lymph nodes, extranodal lesions	• Lymph nodes/nodal masses: Score of 4 or 5 with increased uptake compared to baseline.
	• Extranodal lesions: New FDG avid foci consistent with lymphoma.
		PPD Progression
		An individual node/extranodal lesion must be abnormal (nodal disease with LDi >1.5 cm, extranodal disease with and LDi >1.0 cm) with:
		• Increase of ≥50% from the product of the perpendicular diameters (PPD) from nadir AND
		• Increase in LDi or SDi from nadir
		  • ≥0.5 cm for lesions ≤2 cm
		  • ≥1.0 cm for lesions >2 cm

Nonmeasured lesion	None	Unequivocal progression
Organ enlargement	None	• Progression of pre-existing splenomegaly: Splenic length must increase by 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to 16 cm). • New splenomegaly: Spleen must increase by at least 2 cm from baseline Or • Recurrent splenomegaly
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology	• Regrowth of previously resolved lesions • New node >1.5 cm in any axis • New extranodal site >1.0 cm in any axis • New extranodal site <1.0 cm in any axis or unequivocal/attributable to lymphoma • New assessable disease unequivocal/ attributable to lymphoma of any size
Bone marrow	New/recurrent FDG-avid foci	New or recurrent involvement

FDG: fluorodeoxyglucose; IHC: immunohistochemistry; LDi: longest diameter; N/A: not applicable; PPD: perpendicular diameters; SDi: shortest diameter; SPD: sum of the products of diameters.
Note: It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors),

uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
[1.] Deauville score of 3 will represent a complete metabolic response (Barrington et al., 2014).

14.2. Appendix B: Eastern Cooperative Oncology Group Performance Status Scale

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

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair (Oken et al., 1982).

14.3. Appendix C: Contraception Requirements

Female subjects of childbearing potential must agree to use acceptable, highly effective methods of contraception to avoid pregnancy from the time of signing the informed consent form through at least 12 months after CTX110 infusion.

Nonsterile male subjects who are or may become sexually active with female partners of childbearing potential must agree to use acceptable, highly effective methods of contraception to avoid fathering a child from consent through at least 12 months after CTX110 infusion.

Acceptable methods of contraception for subjects and their partners are listed below. If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before mobilization.
- If the female is of nonchildbearing potential, as described below

Female Subjects

Acceptable, highly effective methods of contraception to avoid pregnancy must be used from consent through at least 12 months after CTX110 infusion.

- Female bilateral tubal ligation performed at least 6 months previously
- Female continuous use of an intrauterine device (non–hormone-releasing or hormone-releasing) for at least 90 days before informed consent
- Female combined (estrogen- and progestogen–containing) or progestogen-only oral hormonal contraception associated with inhibition of ovulation if successfully used for at least 60 days before informed consent or with a second form of approved contraception for at least 60 days after beginning hormonal contraception

Male Subjects

Acceptable contraceptive methods must be used from consent through at least 12 months after CTX110 infusion and include the following:

- Condom with spermicide (either as a single product if commercially available and/or allowed according to local regulations; otherwise condom and spermicide as separate products). Local regulations may require use of an additional acceptable method of contraception.

- Vasectomy (with a negative sperm postvasectomy semen analysis) at least 6 months before start of mobilization, and 1 barrier method of contraception

Acceptable contraceptive methods for female partners of male subjects:

- Bilateral tubal ligation performed at least 6 months previously
- Continuous use of an intrauterine device for at least 90 days before consent
- Hormonal contraceptives, if successfully used for at least 60 days before consent

Additional notes:

- Female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.
- The use of birth control methods does not apply if the female partner has had a bilateral oophorectomy, hysterectomy, or is postmenopausal (as defined below).
- Male subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male subjects must not donate sperm after consent, throughout the study, and for 12 months following CTX110 infusion.
- Unique situations that may not fall within the above specifications may be discussed with the CRISPR medical monitor or designee on an individual basis.

Female Subjects of Nonchildbearing Potential

Female subjects of nonchildbearing potential will not be required to use contraception. To be considered of nonchildbearing potential, female subjects must meet at least 1 of the following criteria:

- Postmenopausal: Female subjects who have been amenorrheic for at least 2 years and have a serum follicle-stimulating hormone level within the laboratory's reference range for postmenopausal females
- Documented hysterectomy and/or bilateral oophorectomy

Note: All other female subjects (including subjects with tubal ligations and subjects who do not have a documented hysterectomy) will be considered to be of childbearing potential.

14.4. Appendix D: Postinfusion Hospitalization

In Part A and Part B, the length of hospitalization post infusion may be extended where required by local regulation or site practice.

14.5. Appendix E: National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0

National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 can be found at the following website: https://evs.nci.nih.gov/ftp1/CTCAE/About.html

Inquiries specifically regarding the Common Toxicity Criteria should be addressed to: ncictephelp@ctep.nci.nih.gov

14.6. Appendix F: B Cell Acute Lymphoblastic Leukemia Response Evaluation

Table 25: B Cell ALL Disease Response

Disease Response	Definition	If Extramedullary Disease is Present at Baseline

Complete remission (CR)	• ≤5% blasts in the bone marrow; and
	• No evidence of disease; and
	• Full recovery of peripheral blood counts (platelets ≥100,000/μL and ANC ≥1,000/μL)
		• Disappearance of measurable and nonmeasurable nodal lesions:
		  • Nodal masses >1.5 cm in GTD at baseline must have regressed to ≤1.5 cm in GTD
		  • Nodes that were 1.1 to 1.5 cm in their long axis and >1.0 cm in their short axis before treatment must have decreased to 1.0 cm in their short axis after treatment
		AND
		• If testes, spleen, and/or liver involvement, they must be normal size by imaging or physical examination
		AND
		• No new lesions

Complete remission with incomplete blood count recovery (CRi)	• ≤5% blasts in the bone marrow; and • No evidence of disease; and • Incomplete recovery of peripheral blood counts (platelets <100,000/μL or ANC <1000/μL)	
Complete remission with partial hematologic recovery (CRh)	• ≤5% blasts in the bone marrow; and • No evidence of disease; and • Partial recovery of peripheral blood counts (platelets ≥50,000/μL, and ANC ≥500/μL)	
Blast-free hypoplastic or aplastic bone marrow	• ≤5% blasts in the bone marrow; and • No evidence of disease; and • Does not meet the criteria for peripheral blood counts for CR, CRi or CRh	
Partial Response	• Meets criteria in blood and bone marrow for CR, Cri, or CRh	• ≥50% decrease in SPD of up to 6 of the largest dominant masses. Dominant masses should be clearly measurable in ≥2 perpendicular dimensions, and should be from different regions of the body if possible AND • No increase in size of liver or spleen by imaging or physical exam AND • If multiple splenic and hepatic nodules are present, they must regress by ≥50% in SPD. There must be a >50% decrease in GTD for a single nodule AND • No new lesions

Disease Response	Definition	If Extramedullary Disease is Present at Baseline
Progressive disease (PD)	• ≥25% increase in absolute number of circulating or bone marrow blasts, or development of extramedullary disease (including CNS disease)	• ≥50% increase from nadir in the sum of the products of at least 2 lymph nodes, or if a single node is involved ≥50% increase in the product of the diameters of this one node; OR • ≥50% increase in the longest diameter of any single previously identified node >1 cm in its short axis; OR • ≥50% increase in size of splenic, hepatic or any other 159onmodal lesion; OR • Development of new lesions
Relapsed disease	• Reappearance of blasts in blood or bone marrow (>5%) after a CR; or • New development of CNS-2 or CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation will be considered a CNS relapse.	
Non-response	• Not fitting the definition of CR, Cri, CRh, blast-free hypoplastic or aplastic bone marrow, or PD, and not having relapsed disease	
Unknown	• Assessment is not done, incomplete, or indeterminate	

ALL: acute lymphoblastic leukemia; ANC: absolute neutrophil count; CNS: central nervous system; CNS-3: total nucleated cell count ≥5 × 10^6/L with blasts on cytocentrifuge; CR: complete remission; CRh: complete remission with partial hematologic recovery; Cri: complete remission with incomplete blood count recovery; GTD: greatest traverse diameter; PD: progressive disease; SPD: sum of the product diameter.
Adapted from National Comprehensive Cancer Network guidelines for treatment of acute lymphoblastic leukemia Version 2.2021(NCCN, 2021).

14.7. Appendix G: Protocol History and Summary of Changes to Protocol CRSPONC001

14.7.1. Summary of Changes to the Current Protocol Version 7.0, Amendment 6 (Global or Rest of World)

The previous version of this protocol (Version 6.0, 30 July 2021) was amended to create the current version (Version 7.0, 12 September 2022). The most significant changes are listed below and all key changes made in the current version of the protocol are summarized in the table below.

- Added Phase 2 to further evaluate the efficacy and safety of CTX110 in subjects with NHL. As a result, reduced the number of subjects in Cohort A Part B (cohort expansion) and moved the interim and final primary efficacy analyses to Phase 2.
- Removed Cohort E (NHL subjects administered CTX110 on Days 1, 8, and 35 with daratumumab in the LD regimen) and Cohort G (adult B Cell ALL subjects with daratumumab in the LD regimen). As a result, reduced the number of subjects in Phase 1 Part A from 162 to 100.
- Revised Phase 1 Cohort B to include subjects who received prior approved autologous CAR T cell therapy.
- Removed N1/N2 stratification for enrollment of subjects with NHL and removed hierarchical analysis.
- Added PMBCL to NHL inclusion criteria
- Removed the inclusion requirement for prior [redacted] (failed, ineligible, or refused) and removed the exclusion criterion "eligible for and agrees to [redacted]
- Updated AE collection periods, reporting procedures, and instructions for reporting disease progression and death.

Change and Rationale	Affected Section(s)
Title Page	
Updated sponsor address due to change in location.	Title Page
Updated study title to indicate addition of Phase 2	Title Page, SYNOPSIS
Introduction	
Updated background on adult B cell ALL CAR T cell therapies to reflect more recent study data and regulatory approval.	Section 1.3, Table 1
Removed the specific number of allogeneic CAR T cell programs in development by the sponsor.	Section 1.5.2
Updated the CTX110 data in the study rationale section to reflect a more recent data cut-off date.	Section 1.8

Change and Rationale	Affected Section(s)
Study Objectives	
Added objectives for the new Phase 2 part of the study. Specified that the primary objective for Phase 1 Part B (cohort expansion) is to assess the preliminary efficacy of CTX110.	SYNOPSIS, Section 2
Subject Eligibility	
Added PMBCL to the types of NHL allowed for inclusion (#3).	SYNOPSIS, Section 3.1, Section 4.1 , Table 3
For subjects with refractory or relapsed disease (#4), removed the requirement for prior [redacted] (failed, ineligible, or refused) in response to regulatory feedback from FDA. Also, removed exclusion criterion #1: Eligible for and agrees to [redacted]	SYNOPSIS, Section 3.1, Section 3.2
Changed the inclusion criteria requirement (#4) for subjects with NHL or adult B cell ALL from 2 or more lines of prior therapy to 2 or more prior therapies to broaden the inclusion.	SYNOPSIS, Section 3.1
In definition of refractory disease (#4), removed the provision that duration of SD up to 6 months is considered refractory disease, as this is not standardly included in the definition of refractory LBCL, per FDA feedback.	SYNOPSIS, Section 3.1
Revised Cohort B to explore CTX110 in subjects with relapse after prior autologous CAR T cell therapy (inclusion criterion #4). Added requirements for prior treatment with approved autologous CD-19-directed CAR T cell therapy, history of response, and toxicity to the therapy and age. Also, added an exception for Cohort B to the exclusion criterion for prior autologous CAR T therapy (#1, formerly #2), and required that subjects in Cohort B demonstrate confirmed CD19 expression. Initial dose to be explored in Cohort B revised to DL4.	SYNOPSIS, Section 3.1, Section 3.2, Table 3, Section 4.1
Revised the exclusion criteria for central nervous system involvement (#5, formerly #6) to clarify which criteria apply to subjects with NHL vs B cell ALL. Also, updated text for subjects with B cell ALL with CNS involvement because the SRC's review after the first 2 patients with CNS are treated (as required in protocol V6.0) has occurred. Subjects with a prior history of CNS involvement with no evidence of current CNS disease during screening and/or those with CNS-2 disease without neurological symptoms are now eligible for the study.	SYNOPSIS, Section 3.2
For therapies that must not be used just prior to study participation (exclusion criterion #12, formerly #13), changed the time window for immune checkpoint therapy and rituximab to be calculated from ~~enrollment~~ CTX110 infusion. Also, specified that hydroxyurea must be stopped ≥72 hours (half-life [2-4 hours]) before CTX110 infusion to minimize overlapping toxicities with this prior treatment.	SYNOPSIS, Section 3.2
Study Design: Investigational Plan	
Added a Phase 2 part of the study to further explore efficacy in cohorts that have been evaluated in Phase 1. As a result, reduced the sample size for Cohort A Part B to up to 30 subjects and moved the interim and final primary efficacy analyses to Phase 2.	SYNOPSIS, Section 1.8, Section 4.1, Section 4.2, minor global revisions
Removed Cohort E and Cohort G, due to the sponsor's decision not to enroll subjects in these cohorts.	SYNOPSIS, Section 3.1, Section 4.1, Section 5,

Change and Rationale	Affected Section(s)
	Section 7, minor global revisions
Added that subjects in Phase 1 Part B or Phase 2 must remain within proximity of the investigative site (i.e.,1-hour transit time) for and at least 14 days for subsequent CTX110 infusions, or longer if justified by subject's clinical status or as required by local regulation or site practice.	SYNOPSIS, Section 4.1.1, Section 4.1.4.3, Section 5.3.2
Revised the number of subjects in Phase 1 Part A from approximately 162 to approximately 100 to reflect the removal of Cohort E and Cohort G	SYNOPSIS, Section 4.1.2, Section 10.4
For clarity, consolidated repeated text within the table into a single footnote: The CTX110 infusion on Day 35 (-7 days/+21 days), if applicable, may be administered without LD chemotherapy if subject is experiencing significant cytopenias (see Section 5.3.1.3.1).	SYNOPSIS, Section 4.1, Table 3
Removed the note for D1 and D2 regarding the SRC review to determine if subjects with B cell ALL with prior history of CNS involvement may be included, as this SRC meeting has already occurred, and these subjects may enroll.	SYNOPSIS, Section 4.1, Table 3
In Cohort D2, added the possibility for a second infusion of CTX110 on Day 35 for subjects who have demonstrated a reduction in detectable MRD and remain MRD positive.	SYNOPSIS, Section 4.1, Table 3, Table 16
Shortened the footnote explanation of legacy Cohort F (discontinued in Version 6.0 of the protocol and merged with Cohort A).	SYNOPSIS, Section 4.1, Table 3
Included DL5 in the rules for dose escalation.	Section 4.1.4
Revised to allow Phase 1 Part B cohort expansion to apply to the adult B cell ALL subcohorts (D1 and D2) (Part B was formerly for NHL cohorts only).	SYNOPSIS, Section 4.1, Section 4.1.5, Section 10.2.1
Allowed for additional subjects (up to 24) to enroll in any Part A cohort (not just any NHL cohort) prior to cohort expansion. Also, clarified that this option to enroll additional subjects up to 24 total applies to each subcohort (e.g., D1 or D2) separately.	SYNOPSIS, Section 4.1, Section 4.1.4
In the description of staggered dosing, made the revision "in subsequent dose levels or ~~expansion of~~ for additional subjects enrolled at the same dose level …" to clarify that this refers to additional Part A subjects, not subjects in Part B cohort expansion. Likewise, revised "~~In expansion of~~ For additional subjects enrolled at the same dose level, cohorts of up to …" in the following paragraph.	SYNOPSIS, Section 4.1.4
To the DLT definitions, added anemia to the list of cytopenias that will be assessed retrospectively, for consistency with the definition of prolonged cytopenias.	SYNOPSIS, Section 4.1.4.2
Updated the protocol to reflect that the recommended Part B dose for Cohort A had been chosen and added a rationale for the decision. Also, moved the explanation of Part B cohort expansion to a higher-level subsection separate from Part A.	Section 4.1.5
Removed the stratification of subjects into the primary population (N1) and bulky-refractor population (N2), per FDA feedback.	SYNOPSIS, Section 4.1, Section 7.1.3
Clarified that the DSMB will ~~perform~~ review the interim analysis in Phase 2.	SYNOPSIS
Study Treatment	
Rephrased the instructions for multiple doses of daratumumab in Cohort C2 who respond to treatment to read: "an additional dose of daratumumab will be administered at the Day 28 visit and an additional infusion of CTX110 will be	SYNOPSIS, Table 3, Section 5.1

Change and Rationale	Affected Section(s)
administered on Day ~~35 and the Day 28~~. A second additional daratumumab dose will be ~~repeated~~ administered as part of the LD regimen for Day 35 unless ~~received~~ within 14 days ~~prior to~~ of the ~~additional CTX110~~ previous Day 28 dose" in order to add clarity based on feedback in the ongoing study.	
Revised the recommendation for LD chemotherapy as follows: "Adult subjects with moderate impairment of renal function (creatinine clearance 30-70 mL/min/1.73 m^2) ~~should~~ may receive a reduced dose of fludarabine in accordance with applicable prescribing information".	Section 5.2
Added Phase 2 LD chemotherapy regimen	Section 5.2
Updated LD chemotherapy rationale to acknowledge inclusion of subjects who received prior treatment with an autologous CD-19 directed CAR T cell therapy and to present supporting data from subjects with prior treatment with a previous allogeneic CAR T cell therapy.	Section 5.2.1
For the CTX110 formulation, removed the brief name of the [redacted] which does not fully describe the product and is subject to change. Updated formulation information is maintained in the CTX110 Investigator's Brochure.	Section 5.3
Updated the rationale for CTX110 additional infusions with more recent study data.	Section 5.3.1.1
In the criteria for Day 35 CTX110 infusions, revised the ICANS criteria to be more stringent, as required by the DSMB. V6.0 criteria • No prior grade ≥2 ICANS following CTX110 infusion that did not resolve (in Cohort E for Day 8 infusion: no prior event of ICANS) V7.0 criteria • Grade 1, 2, or 3 ICANS must have resolved more than 14 days prior to a subsequent CTX110 infusion • No prior grade 4 ICANS	Section 5.3.1.3
In order to reduce the burden on study participants, removed the requirement for tissue biopsy (NHL) or bone marrow sample (B cell ALL) to be obtained whenever possible to demonstrate CD19 expression prior to an additional CTX110 infusion on Day 35.	Section 5.3.1.3
Clarified that in order for subjects to receive an additional CTX110 infusion after PD, the subject must have achieved clinical benefit/response "after the first ~~infusion~~ course of treatment," to allow for a response after a second or third CTX110 infusion in multi-dose regimens.	Section 5.3.1.2, Section 5.3.1.4
Added that the optional second course of treatment will be administered with standard lymphodepletion (i.e., without daratumumab) for subjects in Phase 1 Cohort C, and removed the phrase "consistent with their initial infusion" from the bullets for second course of treatment eligibility criteria to clarify.	Schema, Section 4.1, Section 5.3.1.4
Raised the limit for prohibited corticosteroid therapy from >5 mg/day to >10 mg/day based on relevant clinical trial experience.	Section 5.4.2
Clarified that, while G-CSF is prohibited following CTX110 infusion, "…for cohorts that receive 2 CTX110 infusions with LD chemotherapy in a regimen,	Section 5.4.2, Section 6.2.8

Change and Rationale	Affected Section(s)
proactive use of G-CSF starting ≥10 days following the first CTX110 infusion is strongly recommended to support the second round of LD chemotherapy."	
Toxicity Management	
Per FDA feedback, revised the protocol to require that HLH be diagnosed, managed, and graded separately from CRS. Added diagnosis criteria and guidance specific to HLH.	Section 6.1, Section 6.2.7
For the management of TLS, clarified that the recommendation for prophylactic allopurinol is only for subjects at risk for TLS and that nonallopurinol alternatives, such as febuxostat, should be administered per institutional guidelines.	Section 6.2.3
Revised the CRS management section to remove text related to the previous grading system (Lee 2014) used in previous versions of the protocol, because ASTCT criteria (Lee 2019) are used for CRS grading in all parts of the study as of V6.0. Also, removed "Part A and Part B" from the title of the CRS Grading and Management Guidance because the guidance applies to all parts of the study.	Section 6.2.4, Table 7, Table 8
Reorganized and revised the toxicity management section for neurotoxicity to provide clearer guidance to investigators and to update literature references. Added guidance for differentiating between ICANS and HHV-6 encephalitis and updated Table 12.	Section 6.2.5, Table 10, Table 12
For cytopenia management, clarified instructions regarding frequency of performing a complete blood count with differential in patients with cytopenia grade ≥3 that has not resolved within 28 days of CTX110 infusion. Also clarified proactive use of G-CSF in cohorts that receive 2 CTX110 infusions with LD chemotherapy.	Section 6.2.8, Table 16
For COVID-19 considerations, added that "Whenever possible, a COVID-19 vaccine or booster should not be administered within 4 weeks prior to scheduled imaging for disease assessment" to avoid potential conflict in imaging analysis due to a common side effect of the COVID-19 vaccines: swollen lymph nodes.	Section 6.2.11
Study Procedures	
Added separate rows in the schedule of assessments tables for confirmation of eligibility and enrollment, and an associated footnote, to clarify the sequence of events.	Table 16
In the schedule of assessments, consolidated the rows for tumor biopsy and tumor pathology to clarify that, while the sample may be used for different purposes, this is a single procedure.	Table 16
In the schedule of assessments, added a note in the footnotes to specify that study visits cannot be combined, even if visit windows allow overlap (e.g., D3 ±1 day could overlap with D2 or D5 ±2 days, but separate visits are required for D2, D3, and D5 visits).	Table 16
Revised footnote to clarify that screening assessments should be completed ~~within~~ up to 14 days ~~of~~ after informed consent. Also, allowed for a subject to be rescreened after 3 months of initial consent if specific approval is obtained from the medical monitor.	Table 16
Added double expressor lymphoma to the examples of disease types that are at high risk for CNS involvement	Table 16, Section 7.2.11

Change and Rationale	Affected Section(s)
Clarified that for baseline disease assessment, PET scan/CT should be of diagnostic quality and removed the phrase "with IV contrast." Also added a reference to the imaging manual for details.	Table 16, Section 7.2.15
For BM aspirate/biopsy for NHL subjects, provided clearer direction on which subjects require BM assessment at Day 28 and to confirm CR (BM involvement at screening), and removed the optional assessment for subjects with no BM involvement at screening.	Table 16, Section 7.2.16
Added a reference to the laboratory manual for details on using archival tissue for tumor biopsy at screening.	Table 16
Added a footnote to clarify that all local and central laboratory assessments should be performed prior to dosing, unless otherwise specified. Also, to better accommodate study subjects, added that assessments at Month 6 or later may be delayed or moved ahead of the visit window to accommodate holidays, vacations, and unforeseen delays.	Table 16
Added "if consecutive tests are negative for [redacted] to clarify the example of a reason for the sponsor to request discontinuation of sample collection. Also, added this option to discontinue sample collection to all central laboratory assessments, not just CTX110 PK samples.	Table 16
Clarified that in the event of CRS, additional samples for CTX110 PK and [redacted] should only be collected between scheduled visits. If samples are already being collected as part of a scheduled visit, no additional samples are required to be collected on the same day of the scheduled visit.	Table 16
Added a schedule of assessments for Phase 2 for subjects with NHL with the Phase 1 Cohort A recommended Part B dose and regimen.	Table 17
In the schedule of assessments for Months 30-60, updated the footnote for secondary follow-up to apply to any subject who receives a different line of anti-cancer therapy, not just subjects who undergo stem cell transplant. Also, clarified timing of the first secondary follow-up visit, added requirement for assessments between in-person visits, and added that subjects in secondary follow-up may be moved to a long-term follow-up study under a separate protocol.	Table 18
In the schedule of assessments (Months 30-60), removed the word "blood" from the assessment rows for CTX110 persistence and [redacted] because the assessment may include other samples (e.g., from lumbar puncture or BM biopsy), as detailed in the footnotes. Also added a footnote for the [redacted] assessment to align with the Schedule of Assessments (Screening to	Table 18
In the schedule of assessments (Months 30-60), added rows for survival status and subsequent [redacted] to emphasize the need to perform these assessments.	Table 18
In the schedule of assessments (Months 30-60), applied the footnote that allows the sponsor to request discontinuation of sample collection to [redacted] collection.	Table 18
Clarified that enrollment begins after screening is completed, and that the sponsor's approval of enrollment must occur after the investigator confirms eligibility. Also clarified that screening assessments are to be completed ~~within~~ up to 14 days ~~of~~ after signing the informed consent form. Additionally, specified that subjects should start LD chemotherapy within 7 days after study enrollment.	Section 7.1.1

Change and Rationale	Affected Section(s)
Updated the text for selecting a starting dose to align with text in the synopsis and Section 4.1.4.	Section 7.1.3
Added that subjects who have entered secondary follow-up in this protocol can roll over into the CRISPR long-term follow-up protocol if the long-term follow-up protocol is approved and activated at the investigative site.	Section 7.1.5
Removed the specification that PET/CT scan should be with IV contrast Also, added that additional detail can be found in the imaging manual.	Section 7.2.15
Added that post-baseline imaging will be compared against baseline imaging to determine a response; however, imaging indicative of progression may be compared against the nadir.	Section 7.2.15
Revision to indicate bone marrow biopsy is required at Day 28 in subjects with NHL with BM involvement at screening.	Section 7.2.16
Removed direct bilirubin from the local laboratory tests, as this test was often missed by sites and is not required. For immunological tests, added a footnote to clarify that CD19 and CD20 should be evaluated in the same assay to detect CD19 antigen loss.	Section 7.2.19, Table 19
To [redacted] added the option for collecting prior autologous CAR T cell levels in applicable subjects, due to the revision of Cohort B to enroll subjects with prior autologous CAR T cell therapy.	Section 7.3.5.1
Safety, Adverse Events, and Study Oversight	
Removed the sentence "All AEs will be followed to a satisfactory conclusion" due to ambiguity.	Section 8
AE collection was revised to add the requirement to collect all signs and symptoms of disease progression that meet seriousness criteria (including deaths) for 3 months after CTX110 administration	Section 8.1 , Section 8.7, Table 21, Section 8.10
Clarified that treatment-emergent refers to events (~~occurring post-~~ AEs that start or worsen on or after CTX110 infusion) to align the text with the definition of TEAEs in Section 10.6.2.	Section 8.1
Per FDA feedback, added HLH to the list of AESIs separate from CRS.	Section 8.3
Per EMA feedback, revised the collection of AEs from 3 months after last CTX110 infusion through Month 24 visit to add the collection of nonserious AEs related to LD chemotherapy, study procedure, or CTX110. Also, added a footnote to specify which events are considered related to study procedure and that these events may occur at any time on the study starting at screening.	Section 8.7, Table 21, Table 16, Table 18
Per EMA feedback, revised the collection of AEs from Month 24 to Month 60 visit OR any time a subject starts a new [redacted] to add collection of SAEs and AESIs related to LD chemotherapy and study procedure, not just SAEs and AESIs related to CTX110.	Section 8.7, Table 21, Table 16, Table 18
Clarified that if a subject does not receive CTX110 therapy after enrollment, the AE reporting period ends 30 days after last study-related treatment or procedure	Section 8.7
Updated the AE reporting procedures to reflect a change in vendor. Specifically, replaced contact information for PrimeVigilance with instructions for reporting AEs to the sponsor. Also, added instructions for reporting SAEs or AESIs,	Section 8.8

Change and Rationale	Affected Section(s)
including in the rare event that the investigator does not become aware of the occurrence immediately, as well as the requirement to submit follow-up information in an expedited fashion if requested by the sponsor.	
Revised the disease progression text to align with the new reporting requirement for collection of serious signs and symptoms of disease progression for 3 months after CTX110 administration and with revisions to the AE collection periods. Deleted bulleted text, as both bulleted items are covered elsewhere in the protocol.	Section 8.10
For reporting deaths, added references to relevant safety sections for reporting deaths due to SAEs, and included a new requirement for the use of a Death Report Form for deaths not due to SAEs.	Section 8.11
Stopping Rules and Study Termination	
Clarified the language for Stopping Rules: Deleted: ~~Grade >2 GvHD in subjects who receive [redacted] TCR^{+} cells/kg prior to the initiation of any new~~ [redacted] New: Grade 3 or higher GvHD	Section 9.1
Added stopping rules for Phase 2	Section 9.1
Updated subject numbers required for end of study to reflect the addition of Phase 2.	Section 9.3
Added a section to describe the long-term follow-up study.	Section 9.5
Statistical Analyses	
Updated Statistical Analyses to reflect addition of Phase 2 and deletion of Cohorts E and G including adjustment of objectives, analysis sets, sample size, interim analyses, safety, and efficacy assessment.	Section 10
Deleted ~~Dose Escalation and Cohort Expansion~~ from Secondary Efficacy Endpoints and Exploratory Endpoints headings because these endpoints apply to all parts of the study, including the new Phase 2.	Section 10.2.2 Section 10.2.6
Changed the definition of the safety analysis set to include only subjects who receive CTX110 (not LD chemotherapy and/or daratumumab), i.e., the investigational product, and in accordance with the definition of treatment-emergent AEs in Section 10.6.2.	Section 10.6.2
Appendices	
Removed the original Appendix F: Use of High-dose Vasopressors in CRS Management because it is related to Lee 2014 CRS grading criteria, which are no longer used in the study with the change to Lee 2019 ASTCT criteria. Also removed reference to Appendix F from footnote of Table 7.	Table 7, Section 14
Added blast-free hypoplastic or aplastic bone marrow to the B cell ALL disease response table, in order to add more specificity consistent with other similar clinical trials of ALL.	Section 14.6
Minor editorial and formatting changes were made as applicable throughout for accuracy and consistency.	

14.7.2. Summary of Changes to Protocol Version 6.0, Amendment 5 (Global or Rest of World)

The previous version of this protocol (Version 5.0, 12 February 2021) was amended to create the current version (Version 6.0, 30 July 2021). The most significant changes are listed below, and all key changes made in the current version of the protocol are summarized in the table below.

- Incorporated Cohort F clinical response criteria for additional CTX110 infusion (i.e., CR) into Cohort A and discontinued Cohort F, thus allowing subjects in Cohort A to receive additional CTX110 at SD or better.
- Added Cohort G for adult B cell ALL with inclusion of daratumumab in the lymphodepletion regimen
- Clarified daratumumab may be administered by intravenous infusion or subcutaneous administration.
- Added group sequential hierarchical analysis for Part B cohort expansion with one interim analysis for both efficacy and futility. Added that the interim analysis will be performed when 39 (~50% of 77 subjects in Part Cohort expansion) receive CTX110 infusion and complete 3 months follow-up or discontinue earlier.
- Added that enrollment with be stratified into 2 categories: Primary population (N1) and Bulky-refractory population (N2); defined the populations.
- Simplified FAS definition to be "all subjects who receive CTX110 infusion." Added Treatment-failure-free survival as an efficacy endpoint.
- Revised grading of CRS in both Parts A and B to ASTCT criteria (Lee et al., 2019)

Change and Rationale	**Affected Section(s)**
Title Page	
Updated medical monitor name and contact information.	Title Page
Introduction	
Added newly published data to Table 1 CAR T Cell Clinical Trial Results in ALL and Table 2 Overview of Key Allogeneic CAR T Cell Programs by Other Sponsors.	Section 1.3 and 1.5.1, Table 1, Table 2
Added approvals for lisocabtagene maraleucel.	Section 1.5.1
Replaced summary of Part A preliminary safety data for CTX110 with reference to Investigator's Brochure.	Section 1.8
Study Objectives and Endpoints	
Added recommended Part B dose and cohort to Primary Objective (Part A).	PROTOCOL SYNOPSIS, Section 2, Section 10.1
[redacted]	PROTOCOL SYNOPSIS, Section 2, Section 0, Section 7.3.5.1

Change and Rationale	Affected Section(s)
Clarified that the primary endpoint for cohort expansion applies only to the NHL cohorts (Cohorts A, B, C, and E).	PROTOCOL SYNOPSIS, Section 10.2.1
In secondary efficacy endpoints, added new endpoint of of treatment-failure–free survival; removed event-free survival; removed requirement for central read/assessment for PFS; and clarified that the adult B cell ALL ORR endpoint applies to Cohorts D and G.	PROTOCOL SYNOPSIS, Sections 10.2.2, 10.6.1
Defined [redacted] in an [redacted]	PROTOCOL SYNOPSIS, Section 10.2.6
Subject Eligibility	
Revised Inclusion Criterion #1 to clarify the eligible age for Cohort G.	PROTOCOL SYNOPSIS, Section 3.1
Revised Inclusion Criterion #3 to clarify that Subcohorts C1 and C2 will enroll subjects with histologically confirmed B cell NHL and that Cohort G will enroll subjects with B cell ALL; and that Subcohort G1 is the same as Subcohort D1, and Subcohort G2 is the same as Subcohort D2. Specified that MRD status may also be confirmed by NGS including ClonoSeq.	PROTOCOL SYNOPSIS, Section 3.1
Added Cohort G to the description of refractory or relapsed disease for adult B cell ALL in Inclusion Criterion #4.	PROTOCOL SYNOPSIS, Section 3.1
Specified in Inclusion Criterion #6 that subjects in Cohorts C, E, and G must meet criteria to receive daratumumab.	PROTOCOL SYNOPSIS, Section 3.1
In Inclusion Criteria #8 and #9, specified that acceptable methods of contraception must be used from enrollment through ≥12 months after the most recent CTX110 infusion.	PROTOCOL SYNOPSIS, Section 3.1
In Exclusion Criterion #2, added that the requirement to confirm CD19 expression is optional in Subcohorts D2 and G2.	PROTOCOL SYNOPSIS, Section 3.2
Added new Exclusion Criterion #4 as subjects with the diagnosis of Burkitt's lymphoma/leukemia will not be included in the study 4. Diagnosis of Burkitt's lymphoma/leukemia	PROTOCOL SYNOPSIS, Section 3.2
In Exclusion Criterion #5, clarified that no known contraindication to daratumumab applies to Cohorts C, E, and G.	PROTOCOL SYNOPSIS, Section 3.2
Clarified Exclusion Criterion #6 to allow enrollment of subjects with B cell ALL with CNS-2 disease without neurological symptoms and noted that the SRC will review the first 2 subjects with CNS-2 ALL to determine whether to allow additional subjects with CNS disease. Also specified that subjects with B cell ALL and prior grade 4 neurotoxicity associated with CD19-directed therapy are excluded unless otherwise indicated by the SRC based on safety data from the first 6 subjects with B cell ALL.	PROTOCOL SYNOPSIS, Section 3.2
Specified in Exclusion Criterion #13 that the description of prior therapy for B cell ALL applies to Cohort G in addition to Cohort D. For Cohorts A, B, C, and E, clarified that rituximab, other anti-CD20 monoclonal antibodies, or polatuzumab vedotin must not be used within 30 days prior to enrollment.	PROTOCOL SYNOPSIS, Section 3.2
Added new Exclusion Criterion #18 for Subcohorts D2 and G2 only: Exclusion of isolated extramedullary disease (≤5% blasts in BM and confirmation of presence of clonal blasts in any tissue other than the medullary compartments).	PROTOCOL SYNOPSIS, Section 3.2

Change and Rationale	Affected Section(s)
Study Design: Investigational Plan	
Updated all study schemas to reflect updated study design.	STUDY SCHEMA
Revised table (Table S1 and Table 3) describing lymphodepletion regimen and CTX110 to reflect updated study design.	PROTOCOL SYNOPSIS, Table 3
Incorporated Cohort F into Cohort A and eliminated Cohort F. Cohort F, introduced in Protocol Version 5.0, received LD chemotherapy followed by CTX110 infusion and allowed for reinfusion for subjects who achieved SD, PR, or CR at the Day 28 PET/CT scan. In Protocol Version 6.0, Cohort A allows for a second infusion for all subjects with SD or better, which encompasses the Cohort F regimen.	PROTOCOL SYNOPSIS, STUDY SCHEMA, Table 3, Sections 4.1, 4.1.1, 7, 7.1.3
Added new cohort, Cohort G, to investigate escalating doses of CTX110 with daratumumab + LD chemotherapy in subjects with B cell ALL.	PROTOCOL SYNOPSIS, STUDY SCHEMA, Sections 4.1, 4.1.1, 7, 7.1.3
Clarified that subjects will participate in the study for up to 5 years after the last CTX110 infusion.	PROTOCOL SYNOPSIS, Sections 4.1.1, 4.1.3
Expanded investigation in Part A to escalating doses of CTX110 and different LD regimens and to allow preliminary evaluation of efficacy, as well as safety and PK of CTX110, with or without additional CTX110 infusions.	PROTOCOL SYNOPSIS
Clarified that for cases in which a dose level has been cleared, the sponsor, in consultation with the SRC, may decide to enroll additional subjects at a given dose level. In any dose escalation cohort, 6 additional subjects (up to 12 total subjects) may receive study treatment at or below the highest cleared dose level. Further, with SRC approval, 12 additional subjects (24 total) may receive study treatment in any one NHL cohort (A, B, C, or E) at or below the highest cleared dose level to gather additional safety information prior to cohort expansion.	PROTOCOL SYNOPSIS, Sections 4.1, 4.2
Clarified that dose escalation rules and staggering will apply to all cohorts, and that for subjects who receive additional infusions of CTX110 based on disease response criteria and eligibility, the dose level for the additional CTX110 infusion will be at or below the highest CTX110 dose that has been cleared by the SRC and the sponsor with the planned LD regimen.	PROTOCOL SYNOPSIS, Section 4.2
Clarified that for all cohorts, both LD chemotherapy agents should be started on the same day and administered for 3 consecutive days.	PROTOCOL SYNOPSIS, Table 3, Section 5.2
For Cohort B, removed the exploration of an increased dose of cyclophosphamide.	PROTOCOL SYNOPSIS, Section 4.1
For Cohorts A, B, C2, D1, E, and G1, incorporated an additional CTX110 infusion on Day 35 with LD chemotherapy for subjects who achieve clinical response at Day 28, and noted that this additional CTX110 infusion may be administered without LD chemotherapy if the subject is experiencing significant cytopenias. Also clarified that in Cohort B, the cyclophosphamide dose for the additional CTX110 infusion will be 500 mg/m^2 (vs 750 mg/m^2 used with the initial CTX110 infusion). The DL for the additional CTX110 infusion will be at or below the highest CTX110 doses that has been cleared by the SRC and the sponsor with the planned LD regimen.	PROTOCOL SYNOPSIS, STUDY SCHEMA, Table 3, Table 14, Table 16, Sections 4.1, 5.2, 5.2.1, 5.3.1.2, 5.3.1.3, 5.3.1.3.1, 5.3.1.3.2
Added 1 dose of daratumumab to the LD regimen for Cohorts C, E, and G, administered by IV infusion (16 mg/kg) or SC injection (1800 mg) ≥1 day prior to starting LD chemotherapy and within 10 days prior to CTX110 infusion.	PROTOCOL SYNOPSIS, STUDY SCHEMA,

Change and Rationale	Affected Section(s)
	Table 3, Table 14, Table 16, Sections 4.1, 5.1
Divided Cohort C into Subcohorts C1 and C2. For NHL subjects in Subcohort C1, initial CTX110 infusion on D1 starts at DL3, and subjects who achieve SD or better at the D28 scan receive 2 additional doses of daratumumab at D28 and M2 visits. For Subcohort C2, initial CTX110 infusion on D1 starts at or below the DL cleared in Subcohort C1, and subjects who achieve SD or better at the D28 scan receive a second infusion of CTX110 on D35 with daratumumab and LD chemotherapy. Subjects with adult B cell ALL in Subcohort G2 (BM involvement with <5% blasts) will not receive additional doses of daratumumab at Day 28 (± 4 days) and Month 2 (± 4 days) visits.	PROTOCOL SYNOPSIS, STUDY SCHEMA, Table 3, Sections 4.1, 5.1
Divided Cohort D (B cell ALL) into Subcohorts D1 and D2. Subcohort D1 includes subjects with BM involvement with ≥5% blasts. Initial CTX110 infusion on Day 1 starts at DL2 or DL3, and subjects with a decrease in BM blast count at Day 28 of ≥50% but blast count remains >5% or is MRD-positive receive a second infusion of CTX110 on D35 with LD chemotherapy. Subcohort D2 includes subjects with BM <5% blasts and are MRD-positive (>1 × 10^{-4} cells detected by flow cytometry or PCR or NGS including ClonoSEQ). Initial CTX110 infusion on Day 1 starts at or below the DL cleared in Subcohort D1. No second infusion of CTX110 for subjects in this subcohort.	PROTOCOL SYNOPSIS, STUDY SCHEMA, Table 3, Sections 4.1, 5.1
Revised CTX110 dosing in Cohort E. Second planned dose of CTX110 administered without LD regimen for subjects meeting safety parameters moved to Day 8 (from 3 weeks post initial CTX110). Added third CTX110 infusion on D35 administered with daratumumab and LD chemotherapy for subjects who achieve SD or better at D28 scan.	PROTOCOL SYNOPSIS, STUDY SCHEMA, Table 3, Table 16, Sections 4.1, 5.1, 5.3.1.2, 5.3.1.3, 5.3.1.3.2
Provided details for Cohort G (B cell ALL), which includes Subcohorts G1 and G2. Subcohorts G1 and G2 are defined the same as Subcohorts D1 and D2, respectively.	PROTOCOL SYNOPSIS, STUDY SCHEMA, Table 3
Added that for Cohorts D and G, additional subjects may be enrolled to explore alternative LD dose regimen in which cyclophosphamide may be administered at a dose of 750 mg/m^2 IV daily for 3 days, starting at a CTX110 dose level at or below the highest dose level that has been cleared with LD dose containing cyclophosphamide 500 mg/m^2 IV daily for 3 days and if it has been agreed by the SRC and the sponsor. In that instance, for the second infusion on Day 35 (where applicable), the cyclophosphamide dose in LD chemotherapy will be 500 mg/m^2.	PROTOCOL SYNOPSIS, Table 3
To further evaluate the safety and efficacy of CTX110, allowed parallel cohort expansion (Part B) for any NHL cohorts that have completed dose escalation and have determined the Part B dose per the protocol-specified criteria. Dose escalation for subjects with adult B cell ALL may continue in parallel to cohort expansion for NHL cohorts.	PROTOCOL SYNOPSIS, Sections 4.1, 4.1.1, 4.3
Addition of detailed description of enrollment and safety data as of a data cutoff of 10 April 2021 and discussion of influence on dose rationale for redosing.	Section 5.3.1.1
Study Treatment	
Added option for daratumumab to be administered as 16 mg/kg by IV infusion or 1800 mg by subcutaneous injection.	PROTOCOL SYNOPSIS, STUDY SCHEMA, Table 3, Table 14, Table 16, Sections 4.1, 5.1, 5.1.3

Change and Rationale	Affected Section(s)
Applied list of signs or symptoms that would delay LD chemotherapy for all cohorts to initiation of first daratumumab dose in Cohorts C, E, and G. Clarified the following criterion: Active infection: Positive blood cultures for bacteria, fungus, or virus not responding to treatment, or negative culture but active infection based on investigator judgment in consultation with the medical monitor	PROTOCOL SYNOPSIS, Section 5.2
Included additional criteria for Cohort E regarding signs and symptoms that would prevent administration of the second CTX110 infusion on Day 8.	PROTOCOL SYNOPSIS, Section 5.3.1.3
Clarified that DL3.5 is an optional de-escalation dose level and noted that a DL5 (9×10^8 CAR^+ T cells) may also be explored with SRC approval.	PROTOCOL SYNOPSIS, Table 4, Section 5.3.1.3.2
Defined first and second courses of treatment: First course of treatment: Initial CTX110 infusion with respective LD regimen and the second infusion with LD regimen (Cohorts A, B, C2, D1, and G1) or without LD regimen (Cohort E). In the case of Cohort E, the third CTX110 infusion with or without LD regimen is also part of the first course of treatment. Second course of treatment (optional): For all cohorts, an additional single infusion of CTX110 after PD, administered with LD chemotherapy.	STUDY SCHEMA, Section 4.1
Added alternative premedication methods for daratumumab following discussion with medical monitor, and recommendation for preferential use of intermediate-acting corticosteroids for second or third doses of daratumumab to reduce risk of interference with CTX110.	Section 5.1.1
Expanded rationale for daratumumab dosing to suppress specific NK cells, which may reduce the potential host immune response to allogeneic CAR T cell product and allow increased expansion and persistence of CTX110. Inclusion of supportive data for subcutaneous dosing of daratumumab.	Section 5.1.3
Specified that all subjects in all cohorts will receive LD chemotherapy before additional CTX110 infusions except for the Day-8 CTX110 infusion for Cohort E.	Section 5.2
Added new Section 5.3.1 Additional CTX110 Infusions and provided rationale, administration schedule, and criteria for additional CTX110 infusions, and considerations.	Sections 5.3.1, 5.3.1.1, 5.3.1.2, 5.3.1.3, 5.3.1.3.1, 5.3.1.3.2, 5.3.1.4
Added option to receive an additional infusion of CTX110 infusion with LD chemotherapy after PD if the subject had a prior response.	Table 3, Section 5.3.1.4
Toxicity Management	
Clarified that HLH-observed signs and symptoms are a manifestation of CRS and will not be graded separately.	Section 6.1
Expanded recommendation for herpes zoster and hepatitis prophylaxis to Cohorts C, E, and G. Also recommended pneumocystis jirovecii prophylaxis per local guidelines for subjects receiving multiple CTX110 infusions with LD chemotherapy.	Section 6.2.2
Recommended dexamethasone 10 mg IV every 6 hours for any grade 2 ICANS in subjects with adult B cell ALL (Cohorts D and G).	Section 6.2.5.1, Table 11
To reflect recently published data, added management recommendations for grade 1 ICANS	Table 11

Change and Rationale	**Affected Section(s)**
Clarified that although subjects may meet some of the criteria for HLH or macrophage activation syndrome after CTX110 infusion, this is part of CRS and that given the overlap with CRS, subjects with HLH should also be managed per CRS treatment guidance. Recommended that anakinra or other [redacted] may also be considered following discussion with the medical monitor.	Section 6.2.7
For subjects experiencing grade ≥3 neutropenia, thrombocytopenia, or anemia that has not resolved within 28 days of CTX110 infusion, a complete blood count with differential should be performed weekly until resolution to grade ≤2 or administration of a new systemic [redacted] weekly until Month 3 after each dose of CTX110, then a minimum of monthly until in accordance with institutional practice. Also decreased the amount of time necessary between allowing G-CSF administration for grade 4 neutropenia from 21 to 10 days post–CTX110 infusion, when the risk of CRS has passed; and applied recommendations for monitoring for daratumumab-associated cytopenias to Cohorts C, E, and G.	Section 6.2.8
Study Procedures	
Updated schedule of assessments to reflect revised study design, including updates to Table 16 for assessments specific to Cohort E to reflect the addition of daratumumab and to move the second CTX110 infusion from Day 21 to Day 8.	Table 14, Table 15, Table 16
Added assessment of BCR-ABL1 in peripheral blood if Ph+.	Table 14
Clarified that female subjects of childbearing potential must have a serum pregnancy test performed at the time of screening, and a serum or urine pregnancy test within 72 hours of beginning LD chemotherapy (Cohorts A, B, and D), daratumumab (Cohorts C, E, and G), or additional infusion of CTX110 (Cohorts A, B, C2, D1, E, and G1) when administered without daratumumab or LD chemotherapy.	Table 14, Table 16, Table 17, Section 7.2.5
Updated procedures for subjects who are lost to follow-up and subjects who enter secondary follow-up.	Section 7.1.5
Specified separate timing for ECOG performance status assessment for Cohort E: screening, CTX110 infusion (Day 1), and Day 28 visits.	Table 16, Section 7.2.6
Specified that ECG prior to daratumumab infusion applies to Cohorts C, E, and G and ECG prior to LD chemotherapy applies to Cohorts A, B, and D.	Table 14, Table 16, Section 7.2.8
Added that if relapse occurs during the study, every effort should be made to obtain a biopsy of the relapsed tumor.	Section 7.2.9
Specified that LP is required at screening for all subjects with B cell ALL (Cohorts D and G), and that CSF analysis may be required to confirm CR after CTX110 administration in subjects with B cell ALL with baseline CNS disease.	Table 14, Section 7.2.11
Included additional ICE assessments for Cohort E on Days 10, 12, 14, and 16.	Table 16, Section 7.2.12
Specified that PRO surveys for subjects with B cell ALL will be administered to Cohorts D and G.	Table 14, Table 15, Table 16, Section 7.2.13
Clarified that tumor burden will be quantified at baseline according to Lugano criteria and provided specifics regarding calculating tumor burden assessments.	Section 7.2.15
Added new Section 7.2.15.1 Imaging of Extramedullary Disease in B cell ALL for subjects with B cell ALL with known extramedullary disease at baseline.	Table 14, Table 15, Section 7.2.15.1

Change and Rationale	Affected Section(s)
Removed cell-free DNA testing due to the change in the MRD testing plan for this protocol version, since higher yields from whole blood are preferred over the limited DNA collected from cell-free DNA samples.	Table 14, Table 15, Table 16
Clarified that baseline BM biopsy and aspirate for subjects with NHL can be performed at screening or within 28 days prior to CTX110 infusion, if a recent sample was collected as part of standard of care.	Section 7.2.16
Clarified that baseline BM biopsy and aspirate for subjects with B cell ALL can be performed at screening or within 28 days of CTX110 infusion with appropriate consent, and will be assessed locally to confirm pathology, assess extent of disease, and assign cohorts. Specified that MRD will be assessed locally and centrally, and that subjects in Subcohorts D2 and G2 may be enrolled with local baseline MRD results pending as long as qualifying results within 3 months of enrollment are available.	Section 7.2.18
Added local laboratory test for peripheral blasts in Cohorts D and G for cohort determination.	Table 17
Safety, Adverse Events, and Study Oversight	
Revised CRS grading in both Parts A and B to ASTCT criteria (Lee et al., 2019).	PROTOCOL SYNOPSIS, Table 7, Table 8, Sections 4.2.2, 6.2.4, 10.2.3, 10.6.2
Clarified that for Cohort E, the DLT evaluation period will last for 28 days after the second infusion (Day 8), for a total of approximately 35 days (7 days from initial infusion + 28 days from second infusion). Also clarified that for all cohorts, subjects who receive a subsequent CTX110 infusion on Day 35 and/or after disease progression will be monitored for frequency and severity of AEs and AESIs during the immediate 28-day period after each additional CTX110 infusion in addition to the assessment of safety per the DLT criteria defined in the protocol.	PROTOCOL SYNOPSIS, Sections 4.1.1, 4.2, 10.3
Clarified the DLT definition regarding neurotoxicity: Grade 4 neurotoxicity of any duration that is related or possibly related to CTX110. Also specified that the following should not be considered DLTs: Hypogammaglobulinemia *of any grade* (vs grade 3 or 4 only) For Cohorts D and G: Grade ≥3 cytopenias present at start of LD chemotherapy, pending SRC review and identification of another etiology	PROTOCOL SYNOPSIS, Section 4.2.2
Revised DSMB requirement to include review of any SAEs, including expedited SAEs.	PROTOCOL SYNOPSIS, Section 8.12.2
Specified that for Cohorts D and G, the first 2 subjects at each dose level of Subcohorts D1 and G1 (adult B cell ALL subjects with >5% blasts) will be treated in a staggered manner such that the second subject will only receive CTX110 after the previous subject has completed the DLT evaluation period. However, in Subcohorts D2 and G2 (adult B cell ALL subjects with <5% blasts and MRD+), up to 3 subjects may be enrolled and dosed concurrently if the dose level has been cleared by the SRC in Subcohort D1 or G1, respectively. The opposite will not be allowed. If 3 subjects in Subcohort D2 or G2 are cleared, then Subcohort D2 or G2 alone will advance to the next dose level.	Section 4.2
Clarified that a subject will be replaced and not evaluated for DLT if a subject discontinues the study any time prior to the first CTX110 infusion.	Section 4.2.2

Change and Rationale	Affected Section(s)
Added safety parameters for additional doses of daratumumab.	Section 5.1
Clarified that G-CSF is prohibited following CTX110 infusion but may be administered ≥~~21~~10 days following CTX110 infusion if subject shows no signs of CRS.	Section 5.4.2
To increase subject safety and potentially reduce risk of GvHD, lowered manufacturing threshold from <0.5% TCR^+ cells to ≤0.15% TCR^+ cells in final CTX110 product.	Section 6.2.9
Revised AE definition to reflect GCP E6(R2).	Section 8.1
Clarified that all grade ≥3 infections are to be considered AESIs (vs opportunistic/invasive infections), and that CRS is an AESI, including cases with overlapping manifestations of HLH. Removed HLH as a separate AESI.	Section 8.3
To improve safety data collection, modified timeframe for collection of CTX110-related SAEs, CTX110-related AESIs, and new malignancies as follows: Month 24 to Month 60 visit OR ~~after a subject receives a new [redacted] after Month 3 visit~~ any time a subject starts a new [redacted] d collection of SAEs resulting in death regardless of relationship to CTX110 from Month 24 to Month 60 timeframe	Table 14, Table 15, Table 16, Table 19
Clarified that if additional infusion of CTX110 occurs after the 3-month post–CTX110 infusion period, AE reporting for any additional CTX110 infusion begins with daratumumab or LD chemotherapy administration, as applicable, and that disease progression resulting in death only needs to be reported as an SAE for 30 days after CTX110 infusion (Section 8.10 for exceptions).	Table 19
To ensure comprehensive and timely collection of safety data, deleted the following: Events that are clearly consistent with the expected progression of disease under study and are captured in the eCRF, will be considered as anticipated and not subject to expedited reporting.	Section 8.8
Added new Sections 8.10 and 8.11 to clarify procedures regarding reporting events related to disease progression and deaths, respectively.	Sections 8.10 and 8.11
Clarified that a cohort will be paused in the event of grade >2 GvHD in subjects who receiv [redacted] TCR^+ cells/kg prior to the initiation of any new [redacted]	Section 9.1
Clarified that daratumumab-specific guidance regarding stopping rule for cohorts or subjects applies to Cohorts C, E, and G.	Sections 9.1, 9.2
Statistical Analyses	
Increased sample size of Part A from 6-66 subjects to approximately 162 subjects (approximately 90 subjects with NHL and approximately 60 subjects with B cell ALL), and of Part B from 77 subjects to approximately 97 subjects. Clarified that the sample size estimation for the first cohort expansion will also apply to any subsequent cohort expansions, thus increasing the total number of enrolled subjects in Part B.	PROTOCOL SYNOPSIS, Sections 4.1, 4.1.2, 10.3, 10.4
Defined 2 categories for Part B enrollment: Primary population (N1; approximately 77 subjects): Subjects with SPD <50 cm^2 for target lesions (pre–LD chemotherapy) as assessed by local and/or central	PROTOCOL SYNOPSIS, Sections 4.1, 7.1.3, 10.4

Change and Rationale	Affected Section(s)
analysis, and initiation of first line of [redacted] for subjects with NHL >7 months prior to enrollment. Bulky-refractory population (N2; approximately 20 subjects): Subjects with SPD ≥50 cm^2 for target lesions (pre–LD chemotherapy) as assessed by local and/or central analysis; or initiation of the first line of [redacted] for subjects with NHL ≤7 months prior to enrollment. The maximum number of 20 added subjects with refractory NHL and bulky disease (N2) will not be included in the primary population (N1) to prevent over-representation of subjects with refractory disease with bulky presentation in a cohort and limit the exposure of the investigational product for subjects who are relatively less likely to benefit from it.	
Revised cohort expansion design from optimal Simon 2-stage to an enrichment design with hierarchical testing strategy. Hierarchical hypothesis testing for efficacy will be performed with the first testing in the primary population (N1) and, if positive, followed by a second testing in the total population (N1 + N2) containing both primary and bulky-refractory populations. Group sequential design with alpha-spending function will be employed to test for efficacy in N1.	PROTOCOL SYNOPSIS, Sections 10.4, 10.6.1
Added one interim analysis for futility and efficacy planned when 39 of 77 subjects in the primary population have received CTX110 infusion and completed ≥3 months of follow-up or discontinued earlier. At the interim analysis, the study may be stopped for futility if ≤10 of the first 39 subjects in the primary population achieve objective response (CR or PR); otherwise the study will continue to enroll an additional 38 subjects (total N1 = 77) in the second stage. If ≥20 of the first 39 subjects in the primary population achieve OR, early efficacy can be claimed at the interim analysis.	PROTOCOL SYNOPSIS, Sections 4.1.2, 9.3, 10.4, 10.5.1, 10.6.1
Specified that subjects who have not progressed and are still on study at the data cutoff date will be censored at their last response assessment date. Also clarified secondary efficacy endpoint definitions as follows: DOR: Time between first objective response and first disease progression or death due to any cause <u>after the first objective response.</u> DOCB: Time between first objective response and <u>last</u> disease progression or death ~~that followed the last objective response a subject ever achieved~~. TFFS: Time between first CTX110 infusion and the last disease progression or death due to any cause. Clarified that the secondary efficacy endpoint of ORR for subjects with adult B cell ALL applies to Cohorts D <u>and G</u>.	Section 10.2.2
Appendices	
Linked Appendix F: Use of High-dose Vasopressors in CRS Management to Table 7: Grading of CRS According to ASTCT Consensus Criteria. Added Footnote #2. See Appendix F for information on high-dose vasopressors.	Section 14.6; Appendix F
Updated Appendix G: B Cell Acute Lymphoblastic Leukemia Response Evaluation to include criteria for extramedullary disease present at baseline, partial response, and unknown response.	Appendix G; Table 24
Minor editorial and formatting changes were made as applicable throughout for accuracy and consistency.	

14.7.3. Summary of Changes to Protocol Version 5.0, Amendment 4 (Global or Rest of World)

Version 4.0 (17 June 2020) was amended to create the Version 5.0 (12 February 2021). The country-specific protocol version 4.1 for United States (22 June 2020) has also merged into Version 5.0. The most significant changes are listed below, and all key changes made in the current version of the protocol are summarized in the table below.

- Added 2 new cohorts, Cohorts E and F, to evaluate safety and effect of planned redosing of CTX110 without and with LD chemotherapy in subjects with NHL. Added planned redosing for Cohort A.
- Added new DLT of grade 4 neurotoxicity of any duration that is possibly related to CTX110.
- Added viral encephalitis management.
- Removed the weight threshold from the eligibility criterion (per Version 4.1 United States) with the intent of applying a dose limit of [redacted] TCR^+ cells/kg for all dose levels.
- Added evaluation of changes over time in patient-reported outcomes associated with CTX110 as a secondary study objective.
- Updated definition of a TEAE.
- Modified AE reporting requirements and study time period.

Change and Rationale	**Affected Section(s)**
Removed number of study centers as the number is prone to changes.	PROTOCOL SYNOPSIS
Added secondary objective: To evaluate the changes over time in patient-reported outcomes associated with CTX110 and secondary endpoint: Change over time in patient-reported outcomes	PROTOCOL SYNOPSIS Sections 2, 10.2.5, 10.6.5
Removed requirement for subsequent participation in long-term follow-up trial, and accordingly removed inclusion criterion #10 ("Agree to participate in an additional long-term follow-up study after completion of this study").	PROTOCOL SYNOPSIS Sections 3.1, 4.1.3, 9.3
In inclusion criterion #1, the age limit for Cohort D was raised from 60 to 70 years based on the acceptable safety data observed to date in the clinical study and to facilitate the inclusion of elderly subjects in Cohort D. Also removed weight requirement of >50 kg (from protocol version 4.1 United States) with the availability of a highly sensitive TCR screening assay for CTX110 and given the dose limit of [redacted] TCR^+ cells/kg applicable for all dose levels.	PROTOCOL SYNOPSIS Section 3.1
In inclusion criterion #3, for NHL cohorts clarified that FDG PET positivity is defined by a Deauville score of 4 or 5 on the Lugano criteria 5-point scale.	PROTOCOL SYNOPSIS Section 3.1

Change and Rationale	Affected Section(s)
Updated details of inclusion criterion #3 for Cohort D (histologically confirmed B cell ALL) from "bone marrow involvement with ≥5% blast" to include the following subcohort-specific criteria: D1: Bone marrow involvement with ≥5% blasts (see additional details in Section 4.1) • D2: Bone marrow MRD-positive (defined as $>1 \times 10^{-4}$ cells detected by flow cytometry or PCR) with ≤5% blasts. Removed an element of inclusion criterion #4 for Cohort D (adult B cell ALL) by deleting the following bullet as more details are now included in criterion #3 as specified above: ~~Bone marrow blast <50% at time of screening~~ Removed inclusion criterion #10 ("Agree to participate in an additional long-term follow-up study after completion of this study") since the subject will be asked (not required) to participate in the long-term follow-up study.	PROTOCOL SYNOPSIS Section 3.1
Clarified timing for exclusion criteria #3, #9, #10, and #12 to indicate timeframes are based on time of enrollment, not screening or informed consent. Added the following condition to Exclusion Criterion #5 for subjects with B cell ALL with a prior history of CNS involvement: Subjects with B cell ALL with a prior history of CNS involvement with no evidence of current CNS disease during screening may be included after SRC approval, based on safety data from the first 6 B cell ALL subjects with no CNS disease history treated in the dose escalation part of the study.	PROTOCOL SYNOPSIS Section 3.2 Table 14
Clarified exclusion criterion #6 to specify that disqualifying cerebrovascular ischemia/hemorrhage should be "major."	PROTOCOL SYNOPSIS Section 3.2
To increase subject safety, added "grade 3 or higher pericardial effusion at the time of enrollment" to exclusion criterion #7.	PROTOCOL SYNOPSIS Section 3.2
Revised exclusion criterion #8 as indicated below to clarify parameters for determining if an infection is "uncontrolled": Presence of active bacterial, viral, or fungal infection that is uncontrolled, ~~or requires IV anti-infectives~~ based on investigator judgement in consultation with the medical monitor	PROTOCOL SYNOPSIS Section 3.2
In exclusion criterion #9, expanded allowable timeframe for prior infectious disease testing use in determining eligibility from "within 30 days of signing the ICF" to "within 45 days of enrollment."	PROTOCOL SYNOPSIS Section 3.2
In exclusion criterion #12, clarified that existing information regarding prohibition of systemic antitumor therapy applies to NHL cohorts, and added/expanded exceptions: For Cohorts A, B, C, E, and F (NHL): Use of systemic antitumor therapy or investigational agent within 14 days or 5 half-lives, whichever is longer, of enrollment. Exceptions ~~are made for~~: 1) prior inhibitory/stimulatory immune checkpoint molecule therapy, which is prohibited within 3 half-lives of enrollment; and 2) rituximab use within 30 days prior to ~~screening~~ enrollment is prohibited (however PET/CT needs to occur at least 2 weeks after last rituximab dose). Also added ALL-specific criteria: For Cohort D (adult B cell ALL): Use of systemic antitumor therapy within 7 days of enrollment. Exceptions: 1) immunotherapy agents (i.e., rituximab, inotuzumab) must be stopped within 14 days of enrollment; 2) long-acting chemotherapy agents (e.g., pegylated asperigenase, methotrexate >25 mg/m^2) must be stopped within 14 days of enrollment; and 3) investigational	PROTOCOL SYNOPSIS Section 3.2

<table>
<tr><th>Change and Rationale</th><th>Affected Section(s)</th></tr>
<tr><td>agent must be stopped after 5 half-lives have passed before enrolling. Subjects must have recovered to grade 1 CTCAE from acute toxicity (except hematological) of all previous therapy prior to enrollment. Steroids are permitted until 2 days before starting LD chemotherapy for maintenance or to allow for control of peripheral blood blasts.</td><td></td></tr>
<tr><td>To improve feasibility, added exclusion criterion #16: Life expectancy of less than 6 weeks.</td><td>PROTOCOL SYNOPSIS
Section 3.2</td></tr>
<tr><td>Updated number of subjects in Part A from approximately 6-54 to approximately 6-66 to reflect added cohorts.</td><td>PROTOCOL SYNOPSIS
Sections 4.1.2, 10.4</td></tr>
<tr><td>Updated table summarizing treatment by cohort with the following underlined text to reflect added cohorts and added options for redosing:
<table>
<tr><th>Cohort</th><th>Disease Subset</th><th>Treatment</th></tr>
<tr><td>A</td><td>Adult subjects with DLBCL NOS, high-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, grade 3b FL, and transformed FL</td><td>LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days; completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion
CTX110 starting at DL1
Second planned dose of CTX110 with LD chemotherapy administered 48 weeks after first CTX110 infusion to subjects who achieve SD or PR at Day 28 scan after first CTX110 infusion. Option to redose without LD chemotherapy if subject is experiencing significant cytopenias.
Option to redose CTX110 with LD chemotherapy after PD if subject had prior response</td></tr>
<tr><td>B</td><td>Same as Cohort A</td><td>LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 750 mg/m^2 IV daily for 3 days; completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion
CTX110 starting at ~~DL2~~ DL3
Option to redose CTX110 with LD chemotherapy after PD if subject had prior response</td></tr>
<tr><td>C</td><td>Same as Cohort A</td><td>One dose of daratumumab 16 mg/kg administered at least 1 day prior to starting LD chemotherapy and within 10 days of CTX110 infusion. For subjects who achieve SD or better on Day 28, 2 additional doses of daratumumab (16 mg/kg) will be administered at the Day 28 (± 4 days) and Month 2 (± 4 days) visits. To facilitate administration, the first 16 mg/kg dose may be split (to 8 mg/kg) over 2 consecutive days.</td></tr>
</table></td><td>PROTOCOL SYNOPSIS
Section 4.1
Table 3</td></tr>
</table>

Change and Rationale			Affected Section(s)
		LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days; completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion CTX110 starting at ~~DL2~~ DL3 Option to redose CTX110 with LD chemotherapy after PD if subject had prior response (can redose without daratumumab)	
D	Adult B cell ALL	LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days; completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion CTX110 starting at DL2 or DL3 Option to redose CTX110 with LD chemotherapy after PD if subject had prior response or if subject is MRD-positive	
E	Same as Cohort A	LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days; completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion CTX110 starting at DL3.5 or DL4 Second dose of CTX110 administered without LD chemotherapy 3 weeks after first CTX110 infusion • Option to redose CTX110 with LD chemotherapy after PD if subject had prior response	
F	Same as Cohort A	• LD chemotherapy: Co-administration of fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2 IV daily for 3 days; completed at least 48 hours (but no more than 7 days) prior to CTX110 infusion • CTX110 starting at DL3.5 or DL4 Second dose of CTX110 administered with LD chemotherapy 4-8 weeks after first CTX110 infusion to subjects who achieve SD, PR, or CR at Day 28 scan after first CTX110 infusion. Option to redose without LD chemotherapy if subject is experiencing significant cytopenias. Option to redose CTX110 with LD chemotherapy after PD if subject had prior response	
Per memoranda dated 17 November 2020 and 14 December 2020, increased starting dose levels for Cohorts B and C from DL2 to "DL3." In Cohort A, DL3 (3 × 10^8 CAR$^+$ T cells) was cleared in July 2020 with no DLTs. In total, 5 subjects have been			PROTOCOL SYNOPSIS

Change and Rationale	Affected Section(s)
dosed in DL3, with no CRS, ICANS, or GvHD. Significantly more antitumor activity has been observed at DL3 relative to DL2. For these reasons, the SRC recommended that dose escalation in Cohorts B and C begin at DL3.	Table 3 Sections 4.1, 4.2, 7.1.3
To reflect significantly more antitumor activity observed at DL3 relative to DL2, increased start dose level of Cohorts B and C from DL2 to DL3 and for Cohort D to "DL2 or DL3."	PROTOCOL SYNOPSIS Table 3 Sections 4.1, 4.2
To reflect addition of repeat dosing, specified that follow-up will continue for up to 5 years after the last CTX110 infusion, that subjects must remain within proximity of the investigative site for 28 days after each CTX110 infusion, and that subjects in dose escalation will be hospitalized for the first 7 days following each CTX110 infusion.	PROTOCOL SYNOPSIS Sections 4.1, 4.2.3
Clarified that after Cohort expansion (Part B) will begin with Cohort A at the current version of the protocol to further evaluate the safety and efficacy of CTX110. Regulatory approval will be obtained, where required, prior to enrolling any subjects from that region into cohort expansion. Cohort A expansion may be followed by the expansion of other cohorts, as those complete the dose escalation part of the study, with agreement from the SRC and at the sponsor's discretion.	PROTOCOL SYNOPSIS Section 4.1
To increase subject safety, the dose limit of TCR^+ cells/kg imposed for all dose levels was reduced from 1×10^5 to [redacted] TCR^+ cells/kg, and the weight threshold was removed for the highest dose level, DL4, in any of the cohorts. This dose limit of TCR^+ cells/kg was previously applicable for V4.1 United States.	PROTOCOL SYNOPSIS Sections 4.2, 5.3, 6.2.9
To reflect addition of repeat dosing, specified that the DLT evaluation period begins with initial CTX110 infusion and lasts for 28 days, and that for Cohort E, the DLT evaluation period will last for 28 days after the second infusion (a total of approximately 7 weeks).	PROTOCOL SYNOPSIS Section 4.2
Clarified timing of enrollment and treatment for cohorts as follows: For Cohort A: In DL1 (and DL-1, if required), subjects ~~in each cohort~~ will be treated in a staggered manner, such that the second and third subjects will only receive CTX110 after the previous subject has completed the DLT evaluation period. For Cohorts B, C, D, E, and F: The first 2 subjects within each cohort will be treated in a staggered manner at the starting dose level, such that the second subject will only receive CTX110 after the previous subject has completed the DLT evaluation period. In subsequent dose levels or expansion of the same dose level, cohorts of up to 3 subjects may be enrolled and dosed concurrently.	PROTOCOL SYNOPSIS Section 4.2
Per a memorandum dated 20 November 2020, a new DLT was added based on regulatory feedback regarding a grade 5, possibly CTX110-related neurotoxicity SAE at DL4: Grade 4 neurotoxicity of any duration that is possibly related to CTX110 Also removed grade 4 from the DLT neurotoxicity exception: Grade 3 ~~or 4~~ neurotoxicity (e.g., encephalopathy, confusion) that improves to grade ≤2 within 14 days	PROTOCOL SYNOPSIS Section 4.2.2
Clarified that grade 3 or 4 toxicity that is clinically significant according to the investigator's judgement and does not improve within 72 hours must be CTX110-related to be considered a DLT.	PROTOCOL SYNOPSIS Section 4.2.2
Added revision from a memorandum dated 11 September 2020 that clarified the change to redosing criteria was consistent with the original intent of this language, that a consideration for	PROTOCOL SYNOPSIS

<table>
<tr><th>Change and Rationale</th><th>Affected Section(s)</th></tr>
<tr><td>redosing required conclusive demonstration that CTX110 had antitumor activity in a subject after the first dose. This is typically reflected as an objective response according to the Lugano criteria, which was why the original language references PR or CR. However, specific circumstances may occur when many individual sites of disease respond (e.g., decrease in tumor size and/or FDG-avidity on a PET/CT scan), but a new or worsening lesion leads to an overall determination of PD. In such cases, the investigator may determine a response to CTX110 was achieved and that redosing is appropriate.
Added text in italics:
For all cohorts, a subject may receive a maximum of 3 doses of CTX110. Redosing may occur in 2 scenarios:
1. Planned redosing with or without LD chemotherapy based on timing or disease response criteria: this includes redosing scenarios in Cohorts A, E, and F, as tabulated below
<table>
<tr><th>Cohort</th><th>CTX110 Redosing</th></tr>
<tr><td>A</td><td>Second planned dose of CTX110 administered with LD chemotherapy 4-8 weeks after first CTX110 infusion to subjects who achieve SD or PR at Day 28 scan after first CTX110 infusion. Option to redose without LD chemotherapy if subject is experiencing significant cytopenias.</td></tr>
<tr><td>E</td><td>Second planned dose of CTX110 administered without LD chemotherapy 3 weeks after first CTX110 infusion</td></tr>
<tr><td>F</td><td>Second planned dose of CTX110 administered with LD chemotherapy 4-8 weeks after first CTX110 infusion to subjects who achieve SD, PR, or CR at Day 28 scan after first CTX110 infusion. Option to redose without LD chemotherapy if subject is experiencing significant cytopenias.</td></tr>
</table>
Redosing after progression of disease (PD) if the subject has had initial response after the first CTX110 infusion – includes all cohorts.
Any redosing should be discussed in advance with the medical monitor.
To be redosed with CTX110, subjects must meet the redosing criteria and repeat some of the screening assessments specified in the protocol.
Original:
This study will allow for one-time redosing of NHL subjects with CTX110 based on the investigator's decision in consultation with the CRISPR Therapeutics medical monitor. To be considered for redosing, subjects must have either 1) achieved a PR or CR after CTX110 infusion and subsequently progressed or relapsed within 12 months of the initial CTX110 infusion, or 2) remain in PR (but not CR) at the Month 3 visit.
Confirmation tumor (NHL) or bone marrow (ALL) remains CD19+ at relapse (by flow cytometry or immunohistochemistry).</td><td>Section 4.3.2
Section 4.3.4
Table 15 STUDY SCHEMA</td></tr>
<tr><td>To enhance the effect of CTX110, changed when redosing can occur. For subjects in Cohort A who achieve SD or PR at the D28 scan after the first CTX110 infusion, a second CTX110 infusion will be administered 4-8 weeks after first CTX110 infusion (changed from 3 months postinfusion). Clarified that the earliest time at which a subject could be redosed is ≥3 weeks after initial CTX110 infusion (based on dosing schedule for Cohort E). To increase subject safety, provided option to redose without LD chemotherapy if subject is experiencing significant cytopenias.</td><td>PROTOCOL SYNOPSIS
Sections 4.1.1, 4.3.2
Table 3, Table 15</td></tr>
</table>

Change and Rationale	Affected Section(s)
	STUDY SCHEMA
To provide the benefit of added effect for deep and lasting response, added the option for redosing with CTX110 after PD if the subject had prior response for all cohorts.	PROTOCOL SYNOPSIS Section 4.1.1 Section 4.3.4 Table 3 STUDY SCHEMA
Clarified that <u>for all cohorts, each</u> CTX110 infusion would be delayed if any of the following signs or symptoms are present: • New active uncontrolled infection • Worsening of clinical status compared to prior to start of LD chemotherapy that, in the opinion of the investigator, places the subject at increased risk of toxicity • Grade ≥2 acute neurological toxicity	PROTOCOL SYNOPSIS Section 5.3
Clarified that the existing primary endpoint for cohort expansion (ORR [CR+PR] per Lugano criteria, as determined by IRC) is specifically for Cohort A. Clarified that the primary endpoint for cohort expansion would be determined by independent central ~~radiology~~ review.	PROTOCOL SYNOPSIS Sections 10.2.1, 10.6.1
Added secondary efficacy endpoint of duration of clinical benefit. Duration of clinical benefit (DOCB) will be calculated as the time between the first objective response and the disease progression or death that followed the last objective response a subject ever achieved. Details about the endpoints will be provided in the statistical analysis plan.	PROTOCOL SYNOPSIS Sections 10.2.2, 10.6.1
To provide further context, added Table 2 summarizing other allogeneic CAR T cell programs in clinical development as well as the following text: Overall, initial data demonstrate the safety of the allogeneic CAR T cell approach. Compared to autologous CD19-directed CAR T cell therapy, the incidence of CRS and neurotoxicity remains similar and the events are less severe. In addition, studies of allogeneic CAR T cells demonstrate efficacy similar to that seen with autologous CAR T cells.	Section 1.5.2 Table 2
To provide further context, added information regarding the sponsor's other CAR T cell programs in clinical development.	Section 1.5.2
Provided update on clinical data from Study CRSP-ONC-001.	Sections 1.8, 4.2
Provided a brief information about the addition of new cohorts E and F and added planned redosing for Cohort A. Provided additional details regarding possible expansion of cohorts and enrollment into Cohort D Subcohorts D1 and D2: Cohort D (adult B cell ALL) will enroll subjects within the criteria of 2 subcohorts: D1 will enroll subjects with bone marrow involvement with ≥5% blasts. After 6 subjects are treated, the SRC will review the totality of safety data and determine if any further changes are needed to the inclusion criteria, specifically around blast count before any subsequent subjects are enrolled. D2 will enroll subjects with bone marrow MRD-positive (defined as $>1 \times 10^{-4}$ cells detected by flow cytometry or PCR) with ≤5% blasts.	Section 4.1

Change and Rationale	Affected Section(s)
~~Dose escalation in Cohort D will be conducted separately from the adult NHL study population in Cohorts A, B, C, E, and F.~~	
Added that throughout dose escalation, once a dose has been cleared in a cohort, the sponsor in consultation with the SRC may elect to enroll up to 6 additional subjects at that dose to gather additional safety data. Clarified dose escalation process per cohort and dose level, and that existing CTX110 dose rationale applies to Part A (new Section 4.2.1.1) and added specific rationale for Part B (new Section 4.2.1.2).	Sections 4.2, 4.2.1, 4.2.1.1, 4.2.1.2
Clarified that AEs that have no plausible causal relationship with CTX110 will not be considered DLTs.	Section 4.2.2
Updated rationale for CTX110 redosing (Section 4.3.1) and created new sections providing overall guidance for redosing (Section 4.3.2), planned redosing in NHL cohorts (Section 4.3.3), specific guidance for redosing in Cohorts A, E, and F (Sections 4.3.3.2, 4.3.3.3, respectively), and redosing for all cohorts following PD after initial response (Section 4.3.4).	Sections 4.3.1, 4.3.2, 4.3.3.2, 4.3.3.3, 4.3.4
Clarified that if a subject experiences severe adverse events related to daratumumab, redosing <u>with daratumumab</u> will not be permitted. Added "<u>After at least 3 subjects are treated at a specific CTX110 dose with daratumumab, the sponsor along with the SRC will review the total safety and efficacy data and may decide to enroll additional subjects at a specific dose level with a lower dose of daratumumab (8mg/kg).</u>"	Section 5.1, Table 14
Clarified that G-CSF may only be administered ≥21 days following CTX110 infusion.	Section 5.4.2
To allow investigators more flexibility, added that in the management of grade 1 CRS in Part A, tocilizumab may be considered per investigator's discretion in consultation with the medical monitor.	
Corrected description of grade ≥2 CRS as follows: Subjects who experience grade ≥2 CRS (e.g., hypotension~~, not responsive to fluids,~~ or hypoxia requiring supplemental oxygenation).	Section 6.2.4
Per a memorandum dated 20 November 2020, added information regarding viral encephalitis and lumbar puncture to Sections 6.2.5 and 7.2.11, and created a new section (Section 6.2.5.1) to provide more guidance regarding HHV-6 encephalitis diagnosis and management.	Sections 6.2.5, 6.2.5.1, 7.2.11
Consolidated criteria and guidance for management of ICANS by moving ICE Assessment table from Section 7.2.12 to Section.	Sections 6.2.5.1, 7.2.12
Provided additional guidance for managing hypogammaglobulinemia: IV gammaglobulin will be administered for clinically significant hypogammaglobulinemia (systemic infections<u>, <400 mg/dL</u>) according to institutional standard of care.	Section 6.2.6
Added further guidance for managing HLH: <u>If [CRP and ferritin] laboratory values further support a diagnosis of HLH, CD25 blood levels should be determined in conjunction with a bone marrow biopsy and aspirate, if safe to conduct, for further confirmation. Where feasible, excess bone marrow samples should be sent to a central laboratory. Details of sample preparation and shipment are contained in the Laboratory Manual.</u> Also added the following assessments and clarifications if HLH is suspected: <u>Check for soluble CD25 and triglycerides</u> <u>If possible, perform bone marrow biopsy to assess for hemophagocytosis.</u>	Section 6.2.7

Change and Rationale	**Affected Section(s)**
Given the overlap with CRS, subjects should also be managed per CRS treatment guidance in Table 7 for Part A and Table 9 for Part B. Anakinra may also be considered following discussion with the medical monitor.	
Added further guidance for managing cytopenias. Specified that for subjects experiencing grade ≥3 neutropenia, thrombocytopenia, or anemia that has not resolved within 28 days of CTX110 infusion, a complete blood count with differential must be performed weekly until resolution to grade ≤2. Also added that antimicrobial and antifungal prophylaxis should be considered for any subject with prolonged neutropenia or on high doses of steroids.	Table 14 Section 6.2.8
Created a new section (Section 6.2.11) regarding special consideration during the COVID-19 pandemic.	Section 6.2.11
Removed visit window of ±2d from D2 visit and decreased visit window for D3 visit from ±2d to ±1d.	Table 14
Added PRO assessments to D1, D28, M9, M18, M30, M42, and M54 visits for gathering more frequent and meaningful data in alignment with CTX110 dosing subsequent scheduled visits.	Table 14, Table 15
Clarified that the CT scan used for disease response/assessment should be with IV contrast.	Table 14 Section 7.2.15
Removed CTX110 PK sample collection from M9, M15, and M18 visits that may not be necessary for PK analysis.	Table 14
Removed Sections 7.3.3 [redacted] and 7.3.7 (CTX110) Immunophenotyping) as well as corresponding line items for these assessments in Schedule of Assessments, and blood sample collection for these assessments will now occur on an "as needed" basis as part of [redacted]	Table 14, Table 15 Sections 7.3.5, 7.3.5.1
Clarified that [redacted] analysis should be a [redacted]	Table 14, Table 15, Table 17
To reflect redosing option, revised timeframes for AE collection as follows: Collect all AEs from informed consent to ~~Month 3 visit~~ 3 months after each CTX110 infusion; all SAEs and AESIs ~~after Month 3 visit~~ from 3 months after last CTX110 infusion through to	Table 14, Table 15, Sections 8.7, 10.6.2

Change and Rationale	Affected Section(s)
Month ~~60~~ 24; and CTX110-related AESIs and CTX110-related SAEs, and new malignancies from ~~After~~ Month 24 to Month 60, or after a subject ~~starts~~ receives a new [redacted] Collect SAEs resulting in death regardless of relationship to CTX110 from Month 24 to Month 60 visit. Cross referenced Table 20 tabulating AE collection by study time period in Section 10.6.2.	
Clarified that aspirate in addition to bone marrow biopsy should be collected to confirm CR as part of disease evaluation and may also be collected at time of relapse.	Table 14 Section 7.2.16
Specified that in subjects experiencing signs or symptoms of CRS or neurotoxicity, additional blood samples for CTX110 PK analysis should be drawn per the scheduled outlined in the laboratory manual.	Table 14 Section 7.3.1
Specified that in subjects experiencing signs or symptoms of CRS or ICANS, additional [redacted]samples should be drawn per the schedule outlined in the laboratory manual.	Table 14 Section 7.3.2
Added tumor biopsy upon suspected PD to confirm disease progression.	Table 15
Added sample collection for assessment of cell-free DNA upon disease progression.	Table 15
Removed sample collection for [redacted]assessment from M30, M42, and M54 visits.	Table 15
Clarified that certain assessments for visits after Day 8 may be performed as in-home or alternate-site visits, including assessments for hospital utilization, changes in health and/or changes in medications, body system assessment, vital signs, weight, PRO questionnaire distribution, and blood sample collections for local and central laboratory assessments.	Table 14, Table 15
Added schedule of unique assessments for planned redosing for Cohort E (Table 16)	Table 16
To reflect added cohorts, clarified parameters for subject replacement as follows: During Part B, subjects who withdraw from the study before receiving LD chemotherapy in Cohorts A, B, D, E, or F, or before daratumumab in Cohort C may be replaced.	Section 7.1.4
To reflect added cohorts, clarified timing of pregnancy tests as follows: … and a serum or urine pregnancy test within 72 hours of beginning LD chemotherapy (Cohorts A, B, ~~and~~ D, E, and F), daratumumab (Cohort C), or second dose of CTX110 (Cohort E redosing), including the redosing schedule for respective cohorts.	Section 7.2.5 Table 17
Removed requirement for additional cardiac assessments during grade 3 or 4 CRS to provide investigators with increased flexibility in patient management.	Section 7.2.7
To reflect added cohorts, clarified timing of ECGs as follows: 12-lead ECGs will be obtained during screening, prior to daratumumab infusion (Cohort C only), prior to LD chemotherapy on the first day of treatment (Cohorts A, B, D, E, and F), prior to CTX110 administration on Day 1 (all cohorts), and on Day 28.	Section 7.2.8
Added EQ-5D-5L questionnaire to assess PROs in all cohorts, and FACT-Leu questionnaire to assess PROs in Cohort D.	Section 7.2.13
To reflect redosing option, added that data on hospitalization will be collected during the first 2 months after each CTX110 infusion.	Section 7.2.14
Allowed additional imaging at Month 2 is per investigator discretion for subjects in Cohort E to provide investigators with increased flexibility in patient management.	Section 7.2.15

Change and Rationale	Affected Section(s)
In addition to bone marrow biopsy for NHL, included aspirate sampling to maintain consistency with Laboratory Manual.	Section 7.2.16
Specified that for subjects with adult B cell ALL, bone marrow and aspirate may be assessed for MRD by molecular approaches such as PCR in addition to multicolor flow cytometry.	Section 7.2.18
Specified that instead of [redacted]	Table 17
Provided more detailed information regarding hospitalizations that qualify as an AE or SAE. Original: Interventions for pretreatment conditions (such as elective surgery) or medical procedures that were planned before study participation are not considered AEs. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered AEs. Replaced with: Elective or preplanned treatment or medical/surgical procedures (scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). However, an untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.	Section 8.1
Provided clarification regarding abnormal laboratory results that qualify as an AE. Only abnormal laboratory results considered by the investigator to be clinically significant should be reported as AEs (e.g., an abnormal laboratory finding associated with clinical symptoms, prolonged duration, that requires additional monitoring and/or medical intervention). Whenever possible, these should be reported as a clinical diagnosis rather than the abnormal parameter itself (i.e., neutropenia vs neutrophil count decreased). Abnormal laboratory results without clinical significance ~~(based on the investigator's judgement) are~~ should not ~~required to~~ be recorded as AEs. ~~However, abnormal laboratory findings that result in new or worsening clinical sequelae, require therapy, or adjustment in current therapy are considered AEs and should be graded and reported per CTCAE version 5.0. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.~~	Section 8.1
Provided guidance regarding classification of AEs and hospitalizations as SAEs: ~~The AE is considered by the investigator to be a~~ Other important/significant medical events. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Hospitalization for study treatment infusions, or planned hospitalizations following CTX110 infusion, are not considered SAEs. Furthermore, hospitalizations for observation or prolongation of hospitalization for observation alone should not be reported as an SAE unless they are associated with a medically significant event that meets other SAE criteria as assessed by the investigator.	Section 8.2
Clarified that if the relationship between the SAE and the investigational product is determined to be "possible," a rationale for the assessment must be provided by the reporting investigator.	Section 8.5
Updated the time period for adverse event collection to align with the planned and optional redosings. Also clarified that if a subject starts a new [redacted] after the Month 3 study visit, only CTX110-related SAEs and CTX110-related AESIs, and new malignancies will be reported.	Section 8.7

Change and Rationale	Affected Section(s)
Clarified that events that are clearly consistent with the expected progression of disease under study should be considered as anticipated and not subject to expedited reporting. Progression should be recorded in the eCRF, but the sponsor will not report those events in an expedited manner to the regulatory authorities.	Section 8.8
Updated definition of end of study as follows: The end of the study is defined the time at which the last subject completes the Month 60 visit ~~and enrolls in the long-term follow-up study~~, is considered lost to follow-up, withdraws consent, or dies.	Section 9.3
Added that duration of clinical benefit (DOCB) will be calculated as the time between the first objective response and the disease progression or death.	Section 10.2.2
To reflect option of repeat dosing, updated definition of DLT evaluable set to: All subjects who receive CTX110 and complete the DLT evaluation period or discontinue early after experiencing a DLT. For Cohorts A, B, C, D, and F, the DLT evaluation period will begin with first CTX110 infusion and last for 28 days. For Cohort E, the DLT evaluation period will last for 28 days after the second infusion, for a total of approximately 7 weeks (21 days from initial infusion + 28 days from second infusion). The DES will be used for determination of the recommended Part B dose Updated the FAS to include all subjects who received CTX110 infusion.	Section 10.3
To reflect option of repeat dosing, clarified that the DSMB will review safety data twice a year until the last treated subject in Part B is at least 2 years after-~~treatment~~ last CTX110 infusion.	Section 10.5.2
Updated definition of TEAE. Original: AEs observed after the start of LD chemotherapy (Cohorts A, B, and D) or after the start of daratumumab (Cohort C). Revised: AEs that start or worsen on or after the initial CTX110 infusion. Added reference to Table 20 in Section 8.7 for AE collection by study time period description and deleted this description from Section 10.6.2 for precision and accuracy.	Section 10.6.2
Deleted a country-specific text for hospitalization for 14 days after CTX110 infusion from this version of the protocol and moved to a country-specific version.	Section 14.4 Appendix D
Updated summary of changes and protocol history.	Sections 14.9.1, 14.9.4 Appendix H
Minor editorial and formatting changes were made as applicable.	

14.7.4. Summary of Changes to Protocol CRSP-ONC-001 V4.0, Amendment 3 (Global or Rest of the World)

Protocol CRSP-ONC-001 Version 4.0, 17 June 2020 was created by amending Version 3.0, 10 February 2020. Key changes made in this version of the protocol are summarized below.

Change and Rationale	Affected Section(s)
Added the following language to align the Synopsis and Body of the protocol.	Protocol Synopsis

Change and Rationale	Affected Section(s)
"Dose escalation will be performed using a standard 3+3 design in which 3 to 6 subjects will be enrolled at each dose level depending on the occurrence of dose-limiting toxicity (DLT), as defined in the protocol. The SRC will review available data when the DLT observation period ends for the last subject enrolled in each cohort. The SRC will be responsible for making dose escalation decisions based on review of all available safety pharmacokinetic data. For cases in which dose escalation is permitted, the SRC may alternatively decide to enroll an additional 3 subjects at the current dose level. Based on ongoing assessment of benefit and risk, the SRC may stop dose escalation before a maximum tolerated dose (MTD) is determined."	
Updated the total CAR^+ T cell dose to be administered in Dose Level 4 of Part A to 6 $\times 10^8$ since a full log increase between Dose Levels 3 and 4 was considered unattainable by the SRC and sponsor. Original "$1x10^9$"	Protocol Synopsis, Table 4
Added guidelines for de-escalation to $4.5x10^8$ total CAR+ T cell dose to ensure patient safety in the higher dose escalation dose levels: "Data from DL3 will be evaluated by the SRC to determine whether dose escalation will continue with DL4. If 1 of 3 subjects in DL4 experiences a DLT, the SRC and sponsor may expand to treat 3 more subjects at DL4 or de-escalate to a lower dose level consisting of $4.5x10^8$ CAR+ T cells."	Protocol Synopsis, Section 4.2
Clarified that the grading and management of CRS will use the Lee et al.,014 criteria in Part A and the American Society for Transplantation and Cellular Therapy (ASTCT) criteria (Lee et al.,2019) in Part B. At the time of the original protocol version (V1.0), the well-known Lee et al., 2014 CRS grading criteria was applied. However, this has been updated to the ASTCT criteria (Lee et al., 2019), which has become the worldwide standard for CRS grading. Therefore, the sponsor plans to use the ASTCT criteria during Part B (cohort expansion) of the trial. The sponsor will continue to use both published CRS grading criteria (Lee et al., 2014, Lee et al., 2019) for future reporting of CRS. Added the following tables for the grading and management of CRS in Part B: Table 8: Grading of CRS According to the ASTCT Consensus Criteria (Lee et al., 2019) – Part B Table 9: CRS Grading and Management Guidance – Part B	Protocol Synopsis, Section 4.2.2, Section 6.2.4, Section 6.2.7, Section 10.2.3, Section 10.6.2
Added that this study will allow for one-time redosing of subjects (NHL) with CTX110 based on the investigator's decision in consultation with CRISPR Therapeutics medical monitor. To be considered for redosing, subjects must have either 1) achieved a PR or CR after CTX110 infusion and subsequently progressed or relapsed within 12 months of the initial CTX110 infusion, or 2) remain in PR (but not CR) at the Month 3 visit. The earliest time at which a subject could be redosed is ≥2 months after the initial CTX110 infusion. Added the redosing criteria and Stage 1 screening assessment that must be repeated for redosing Added that all other visits (starting with Stage 2) should be performed as per the Schedule of Assessments (Table 14) consistent with their initial dosing. Subjects in the dose escalation cohort (A, B, or C) who undergo redosing with CTX110 will receive the same lymphodepletion regimen (Stage 2) as (a) identical to that previously received, or (b) subsequently cleared during dose escalation. Subjects in the expansion cohort will be redosed with the recommended Part B dose.	Protocol Synopsis, Section 4.3, Section 4.3.1, Table 15, Section 13

Change and Rationale	Affected Section(s)
Provided the rationale for redosing CTX110 in a subsection (Section 4.3.1). Given the clinical safety data with CTX110 to date, and the proof of concept demonstrated by similar therapies that show redosing of allogeneic CAR T can induce objective responses, the sponsor proposes to include redosing in this protocol for subjects that meet specific criteria designed to protect subject safety.	
Updated the neurotoxicity grading reference to Lee et al.,2019. Lee et al.,2018 referred to the article in press. Original "Lee et al. 2018" Replaced ASBMT with ASTCT consensus recommendations. Mentioned that ASTCT was formerly known as American Society for Blood and Marrow Transplantation, ASBMT.	Section 4.2.2, Section 6.2.4, Section 6.2.5, Section 10.6.2, Section 13
Removed the sentence "The infusion of each vial should occur within 20 minutes of thawing." since the specifics are covered in the infusion manual. "CTX110 consists of allogeneic T cells modified with CRISPR-Cas9, [redacted] ~~The infusion of each vial should occur within 20 minutes of thawing~~. Infusion should preferably occur through a central venous catheter. A leukocyte filter must not be used."	Section 5.3
Added "In addition to treatment guidelines provided in Table 12Table 11, nonsteroidal agents (e.g., anakinra, etc.) may be considered for ICANS management after discussion with the CRISPR medical monitor (Neill et al., 2020)."	Section 6.2.5
Added the following statement in case of severe cytopenias observed with higher cyclophosphamide or daratumumab infusion "G-CSF administration may be considered earlier but must first be discussed with the medical monitor."	Section 6.2.8
Updated the AE, SAE, and AESI collection guidelines: "All SAEs and AESIs should be reported for up to 3 months after CTX110 infusion if a subject starts a new [redacted] before Month 3 study visit. After Month 3 study visit if a subject starts a new [redacted] only SAEs and AESIs related to CTX110 will be reported. If a subject does not receive CTX110 therapy after enrollment, the AE reporting period ends 30 days after last study-related procedure (e.g., biopsy, imaging, LD chemotherapy). Original "If a subject begins new [redacted] before Month 3 study visit, only SAEs and AESIs should be reported for up to 3 months after CTX110 infusion. Only AESIs will be reported if a subject begins new [redacted] after Month 3 study visit. If a subject does not receive CTX110 therapy after enrollment, the AE reporting period ends 30 days after last study-related procedure (e.g., biopsy, imaging, LD chemotherapy). … Deleted the redundant information (Section 8.7) shown in strikethrough. The information exists in the updated Table 18 ~~"All SAEs and AESIs, whether or not they are considered related to the investigational product, must be reported.~~ SAEs and AESIs must be reported to PrimeVigilance within 24 hours of the first awareness of the event."	Table 14, Footnote 12 Section 8.7, Section 8.8

Change and Rationale	Affected Section(s)
Updated footnote 29 of the Schedule of Assessments to: Clarify that Day 1 PK samples should be collected prior to CTX110 infusion on Day 28 and M2 prior to each daratumumab redosing. Added that samples for [redacted] assessment will be collected at the same specified time as that for the PK sample.	Table 14
Updated the analysis sets to the following: "Part A (Dose Escalation) DLT evaluable set (DES): All subjects who receive CTX110 and are followed for at least 28 days postinfusion or discontinue early after experiencing a DLT. The DES will be used for determination of the recommended Part B dose. Part A + Part B (Dose Escalation + Cohort Expansion) Enrolled set: All subjects enrolled in the study. The Enrolled set will be classified according to the assigned dose level of CTX110. Treated set: All subjects who received any study treatment in the study. The subjects in the Treated set will be classified according to the received study treatment. Full analysis set (FAS): All subjects who received CTX110 infusion and had the opportunity to be followed for at least 3 months (i.e., completed at least 3 months follow-up or discontinued prior to data cut-off). The subjects in FAS will be classified according to the assigned dose level of CTX110. The FAS will be the primary analysis set for clinical activity assessment. Safety analysis set (SAS): All subjects who received CTX110 infusion. The subjects in SAS will be classified according to the received dose level of CTX110. The SAS will be the primary analysis set for the characterization of CTX110 safety profile. Original "Part A (Dose Escalation) DLT evaluable set: All subjects who receive CTX110 and are followed for at least 28 days postinfusion or withdraw consent after experiencing a DLT Part A + Part B (Dose Escalation + Cohort Expansion) Full analysis set (FAS): All subjects who are enrolled and receive CTX110 infusion and have baseline and at least 1 post-baseline disease assessment. The subjects in FAS will be classified according to the assigned dose level of CTX110. The FAS will be the default analysis set for clinical activity assessment. Safety analysis set (SAS): All subjects who are enrolled and receive study treatment. The subjects in SAS will be classified according to the received study treatment. The SAS will be the default set for safety analyses."	Section 10.3
Separated analyses in Section 10.6.3 into. 2 sections, 1 for Pharmacokinetic and Pharmacodynamic Analyses (Section 10.6.3) and another for [redacted] to represent information appropriate for respective sections.	Section 10.6.3 Section 10.6.4
Updated summary of changes and protocol history.	Section 14.9 (Appendix H), Section 14.9.4
Minor editorial and formatting changes were made throughout as applicable.	

14.7.5. Protocol History

Document/Version	Date	Global/Country/Site Specific
Original Protocol/Version 1.0	06 February 2019	Global
Amendment 1/Version 2.0	06 May 2019	Global
Amendment 2/Version 3.0	10 February 2020	Global
Amendment 3/Version 4.0	17 June 2020	Global
Amendment 4/Version 5.0	12 February2021	Global
Amendment 5/Version 6.0	30 July 2021	Global
Amendment 6/Version 7.0	12 September 2022	Global

14.8. Appendix H: Signature Pages

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol	CRSP-ONC-001
Title	A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety and Efficacy of Anti-CD19 Allogeneic CRISPR-Cas9–Engineered T Cells (CTX110) in Subjects With Relapsed or Refractory B Cell Malignancies
Date	12 September 2022
Version	7.0
Amendment	6

Reviewed and Approved by:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 12-Sep-2022 | 9:04 AM EDT
[redacted]

[redacted]
Medical Monitor
CRISPR Therapeutics AG

Date

PROTOCOL ACCEPTANCE FORM

Protocol	CRSP-ONC-001
Title	A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety and Efficacy of Anti-CD19 Allogeneic CRISPR-Cas9–Engineered T Cells (CTX110) in Subjects With Relapsed or Refractory B Cell Malignancies
Date	12 September 2022
Version	7.0
Amendment:	6

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), and all applicable regulatory requirements.

Investigator's Signature _____ Date _____

Name (printed) _____