# STATISTICAL ANALYSIS PLAN

## 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

## CLINICAL STUDY PROTOCOL CRSP-ONC-001

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# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALL | Acute Lymphoblastic Leukemia |
| BOR | Best Overall Response |
| CAR | Chimeric Antigen Receptor |
| Cas9 | CRISPR-associated protein 9 |
| CI | Confidence Interval |
| CR | Complete Response |
| CRF | Case Report Form |
| CRISPR | Clustered Regularly Interspaced Short Palindromic Repeats |
| CRS | Cytokine Release Syndrome |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DES | DLT Evaluable Set |
| DLBCL | Diffuse Large B-cell Lymphoma |
| DLT | Dose-limiting Toxicity |
| DSMB | Data Safety Monitoring Board |
| DOR | Duration of Response |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| FAS | Full Analysis Set |
| FL | Follicular Lymphoma |
| GvHD | Graft versus Host Disease |
| HSCT | Hematopoietic Stem Cell Transplant |
| ICANS | Immune Effector Cell–associated Neurotoxicity Syndrome |
| ICF | Informed Consent Form |
| LD | Lymphodepletion |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRD | Minimal Residual Disease |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| NCCN | National Comprehensive Cancer Network |
| NHL | Non-Hodgkin lymphoma |

| Abbreviation | Term |
|---|---|
| ORR | Objective Response/Remission Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PFS | Progression-Free Survival |
| PK | Pharmacokinetic(s) |
| PR | Partial Response |
| PT | Preferred Term |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Safety Analysis Set |
| SD | Stable Disease |
| SOC | System Organ Class |
| SPD | Sum of Products of Perpendicular Diameters |
| SRC | Safety Review Committee |
| TEAE | Treatment-Emergent Adverse Event |

# 1. INTRODUCTION

This statistical analysis plan (SAP) describes the analysis for 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" version 7.0 (amendment 6) which was issued on 12 September 2022. The enrollment for the study was discontinued as of the time of the SAP amendment. This SAP provides a description of the strategy, rationale, and statistical techniques to evaluate the key safety, efficacy, and pharmacokinetics (PK) endpoints to support an abbreviated clinical study report (CSR).

# 2. KEY STUDY OBJECTIVES

## 2.1. Phase 1

### 2.1.1. 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.
- **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).

### 2.1.2. Secondary Objectives (dose escalation and cohort expansion)

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

## 2.2. Phase 2

### 2.2.1. Primary objective

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

### 2.2.2. Secondary objectives

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

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design

Study CRSP-ONC-001 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. 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 gene editing components. The study includes a Phase 1 and a Phase 2. Phase 1 of the study is divided into 2 parts: a dose escalation part (Part A) and a cohort expansion part (Part B). Part A is to primarily evaluate the safety of escalating doses of CTX110 and identify cohort and CTX110 dose for expansion. Part B is to further evaluate the safety and preliminary efficacy of CTX110 at a recommended Part B dose level and regimen in non-Hodgkin lymphoma (NHL) subjects. Following dose escalation and expansion of Phase 1 Cohort A, the sponsor began enrollment in Phase 2 to evaluate efficacy and safety of CTX110 at the recommended dose level and regimen for Cohort A. As of the time of the SAP amendment, Phase 1 of the study has completed, and the enrollment for Phase 2 was discontinued at the sponsor's discretion.

During both Phase 1 and Phase 2, the study consists 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 below for treatment by cohort (Table 1).

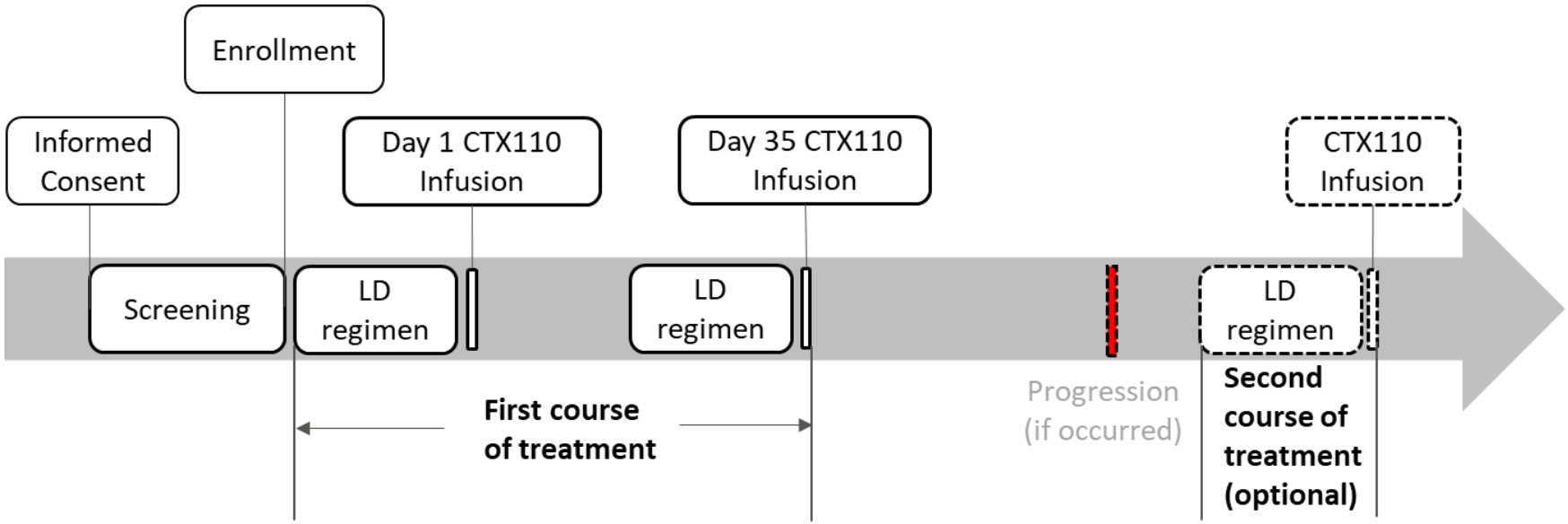
**Stage 3**: Follow-up for all cohorts (up to 5 years after the last CTX110 infusion).

This study allows up to 2 courses of CTX110 treatment (Figure 1):

- The first course of CTX110 treatment includes the first CTX110 infusion on Day 1 and the second CTX110 infusion on Day 35 (-7 days/+21 days) in selected cohorts (A, B, C2, D) for subjects who have not progressed at Day 28 disease assessment and have demonstrated clinical benefit from the initial dose (Table 1). Subjects in Cohort C1 will not receive a second CTX110 infusion at Day 35. Lymphodepletion (LD) chemotherapy consisting of cyclophosphamide and fludarabine will be administered daily for 3 days as an IV infusion prior to each CTX110 infusion. However, LD chemotherapy prior to the Day 35 CTX110 infusion can be omitted if a subject has a platelet count <25,000 cells/μL or ANC <500/mm$^3$. The subjects in Cohort C will additionally receive daratumumab prior to LD chemotherapy.
- Subjects who have demonstrated clinical benefit after the first course of treatment but subsequently progress may qualify for an optional second course of CTX110 infusion preceded by LD chemotherapy. This second course of therapy must be provided within 18 months of the first CTX110 infusion and ≥4 weeks from the prior CTX110 infusion.

Details of CTX110 administration can be found in Section 5.3 of the study protocol.

**Figure 1: The first course of treatment and the optional second course of treatment**




Lymphodepletion (LD) regimen includes LD chemotherapy (fludarabine + cyclophosphamide) for all cohorts, and additional daratumumab for cohort C (Section 3.1.1 of the SAP).
Day 35 CTX110 infusion is not applicable to subcohort C1 (Section 3.1.1 of the SAP).
If a subject achieves initial response to the first course of treatment but subsequently progresses, the subject will have the option to receive a second course of treatment.

A study Safety Review Committee (SRC) consisting of investigators and sponsor representatives reviewed all available safety data and made decisions regarding dose escalation to determine the Recommended Part B Dose (RPBD) for cohort expansion. The SRC continued to meet regularly during the expansion part to discuss toxicity management algorithms and to review individual subject cases.

An independent Data Safety Monitoring Board (DSMB) reviewed expedited reports of any serious adverse events, and aggregate safety data twice a year. The DSMB also reviewed and endorsed the RPBD before subjects were enrolled in cohort expansion part.

More details about study design can be found in the study protocol.

### 3.1.1. Overview of Phase 1

#### 3.1.1.1. Dose escalation (Part A)

Dose escalation (Part A) investigated escalating doses of CTX110 in multiple independent cohorts (Cohorts A, B, C and D).

These cohorts allowed preliminary evaluation of the safety and pharmacokinetics of CTX110 when used with different lymphodepletion regimens as summarized in the following table (Table 1).

**Table 1: Lymphodepletion Regimen and CTX110 Infusion Schedule (Phase 1 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**<br>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.<br>**Stage 2B**<br>• Initial CTX110 infusion on Day 1 starting at DL1<br>• 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**<br>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. |

| Cohort | Disease Subtype | First Course of Treatment |
|---|---|---|
| | | **Stage 2B**<br>• Initial CTX110 infusion on Day 1 starting at DL4<br>• A second infusion of CTX110 on Day 35 (-7 days/+21 days) with LD chemotherapy (co-administration of fludarabine 30 mg/m2 + cyclophosphamide 500 mg/m2 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**<br>LD regimen: Daratumumab + LD chemotherapy<br>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.<br>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.<br>**Stage 2B**<br><u>Cohort C1</u><br>• Initial CTX110 infusion on Day 1 starting at DL3<br>• No second infusion of CTX110 on Day 35<br>• 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.<br><u>Cohort C2</u><br>• Initial CTX110 infusion on Day 1 starting at or below the DL cleared in Cohort C1<br>• 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). |

| Cohort | Disease Subtype | First Course of Treatment |
|---|---|---|
| **D** (Subcohorts D1 and D2) | Adult B cell ALL<br>D1: BM involvement with ≥5% blasts.<br>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**<br>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]<br>**Stage 2B**<br><u>Cohort D1 (BM involvement with ≥5% blasts)</u><br>• Initial CTX110 infusion on Day 1 starting at DL2 or DL3<br>• 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.<br><u>Cohort D2 (BM involvement with <5% blasts and MRD-positive)</u><br>• CTX110 infusion on Day 1 starting at or below the DL cleared in D1<br>• 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: lymphodepletion; 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.
Subjects in legacy Cohort F (discontinued in Version 6.0 of the protocol) have been merged with Cohort A.
* Cohort B enrolled subjects only at selected investigative sites, at the sponsor's discretion.

Cohort F, introduced in Protocol Version 5.0, was discontinued in Protocol Version 6.0. Cohort F included a second infusion for subjects who achieved SD, PR, or CR at Day 28 visit. In Protocol Version 6.0, Cohort A allowed for a second infusion during the first course of treatment for all subjects with SD or better at the Day 28 visit, which encompasses the criteria for the Cohort F regimen. Cohort F subjects will be included in Cohort A for analyses.

For all cohorts, a subject may receive a second course of treatment in the event of initial response and subsequent disease progression, as described in Section 3.1 of the SAP.

Dose escalation was performed using a standard 3+3 design in which 3 to 6 subjects were enrolled at each dose level depending on the occurrence of dose-limiting toxicities (DLTs) during DLT period. A study Safety Review Committee (SRC) reviewed all available safety data and made decisions regarding dose escalation (or de-escalation) and determined the recommended part B dose (RPBD). An independent Data Safety Monitoring Board (DSMB) reviewed and endorsed the RPBD.

The following doses of CTX110, based on the total number of CAR+ T cells, may be evaluated in this study, beginning with Dose Level 1 for Cohort A (Table 2). Dose levels 1-4 (including Dose Level 3.5) were explored, and no subject was enrolled for Dose Level -1 or 5. CTX110 dose level 4 ($6\times10^8$ CAR+ T cells) with two-infusion regimen (Day 1 and Day 35 infusion) was selected as the recommended Part B dose level and regimen.

**Table 2: Dose levels of CTX110**

| Dose Level | Total CAR+ T Cell Dose |
|---|---|
| -1 (de-escalation) | $1\times10^7$ |
| 1 | $3\times10^7$ |
| 2 | $1\times10^8$ |
| 3 | $3\times10^8$ |
| 3.5* | $4.5\times10^8$ |
| 4 | $6\times10^8$ |
| 5** | $9\times10^8$ |

* DL3.5 is an optional de-escalation dose level from DL4.
** The sponsor, with approval of the safety review committee, may explore DL5 in parallel to cohort expansion.

#### 3.1.1.2. Cohort expansion (Part B)

Cohort expansion (Part B) enrolled more subjects in Cohort A to further evaluate the safety and efficacy of CTX110 in NHL subjects at the recommended CTX110 dose level and regimen. As of the time of the SAP amendment, the enrollment for Part B was completed.

### 3.1.2. Overview of Phase 2

Following dose escalation (Part A) and cohort expansion (Part B) of Phase 1, the sponsor began the enrollment in Phase 2 to evaluate efficacy and safety of CTX110 in a larger population of subjects with NHL in Cohort A at the recommended dose level and regimen determined in Phase 1. The enrollment in Phase 2 was discontinued at the sponsor's discretion, and 8 subjects were enrolled at the time of discontinuation.

### 3.1.3. Overview of Plans for Data Analysis and Abbreviated Clinical Study Report

The key study data will be analyzed and reported in an abbreviated clinical study report (CSR) based on all subjects' data from Phase 1 and Phase 2.

## 3.2. Study Measures and Endpoints

### 3.2.1. Efficacy Measures and Endpoints

The efficacy of CTX110 in NHL subjects was assessed per 2014 Lugano criteria for lymphoma (Cheson et al., 2014) (Appendix 14.1 in the study protocol). The efficacy of CTX110 in ALL subjects was assessed per B-Cell Acute Lymphoblastic Leukemia (ALL) Response Evaluation Criteria adapted from 2021 National Comprehensive Cancer Network (NCCN) guidelines for treatment of acute lymphoblastic leukemia Version 2 (Appendix 14.6 in the study protocol). Efficacy analyses will be based on local efficacy assessments by investigators.

The following efficacy endpoints will be summarized.

Objective response/remission rate (ORR):

ORR for NHL is defined as the rate of best overall response of complete response (CR) or partial response (PR) per 2014 Lugano response criteria.

ORR for ALL is defined as the rate of best overall response of complete remission (CR) or complete remission with incomplete blood count recovery (CRi) per B-Cell ALL Response Evaluation Criteria adapted from 2021 NCCN guidelines for treatment of acute lymphoblastic leukemia Version 2 (NCCN Guidelines ALL, v2, 2021).

Complete response/remission rate (CRR):

CRR is defined as the rate of complete response/remission (CR) per protocol-specified response criteria for NHL and ALL, respectively.

[redacted]:

[redacted]

Duration of response (DOR) for NHL:

Among subjects who achieved objective response (CR or PR for NHL), DOR will be calculated as the longest time interval from an occurrence of objective response (OR) to the first disease progression or death, whichever occurred first, following the OR. Responders without progression or death will be censored at the last adequate response assessment prior to any post-CTX110 alternative anti-cancer therapy.

Progression-free survival (PFS) for NHL:

PFS will be calculated as the time interval from the first CTX110 infusion to the first disease progression or death, whichever occurred first. Subjects without progression or death will be censored at the last adequate response assessment prior to any post-CTX110 alternative anti-cancer therapy.

Overall survival (OS) for NHL:

OS is defined as the time interval from the first CTX110 infusion to death due to any cause. Subjects who are alive at the analysis cut-off date will be censored at the last known alive date.

### 3.2.2. Safety Measures and Endpoints

Safety will be evaluated by the following:

- Reporting of adverse events (AEs), including determination of DLTs, serious adverse events (SAEs), treatment-related AEs, AEs leading to discontinuation and AE of special interest (AESI). The severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 except for Cytokine Release syndrome (CRS) (ASTCT Criteria), neurotoxicity (ICANS and CTCAE) and Graft versus Host Disease (GvHD) (MAGIC Criteria). More details about grading for AE severity can be found in Section 8.4 of the study protocol. Frequency of adverse events by severity and relationship will be summarized.
- Reporting of safety laboratory parameters, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

### 3.2.3. Pharmacokinetics Measures and Endpoints

Levels of CTX110 as anti-CD19 CAR DNA in peripheral blood will be summarized.

### 3.2.4. Patient-Reported Outcome Endpoint

Change over time in patient-reported outcomes (PROs) associated with CTX110 (Section 7.2.13 of the study protocol) was planned as a secondary endpoint of the study.

The PRO data collected are sporadic, and they will not be analyzed or reported in the abbreviated CSR.

## 3.3. Sample Size Estimation

### 3.3.1. Phase 1

Based on the planned dose escalation procedure (Section 3.1.1 of the SAP), it was estimated that approximately 100 (70 NHL and 30 ALL) subjects would be enrolled for the multiple cohorts in dose escalation (Part A) during Phase 1 of the study. Dose escalation was performed using a standard 3+3 design where 3 to 6 subjects were enrolled at each dose level depending on the occurrence of DLTs. At least 6 subjects needed to be administered in the study before a Recommended Part B Dose (RPBD) can be declared. Meanwhile, additional subjects could be enrolled during dose escalation, for the replacement of subjects who withdrew or were lost to follow-up before completing the DLT evaluation period.

Cohort expansion (Part B) began with Cohort A to further evaluate the safety and efficacy of CTX110 in NHL subjects. The sample size of Cohort A in Phase 1 Part B (cohort expansion) was capped at 30.

As of the time of the SAP amendment, the enrollment for Phase 1 has completed, and a total of 85 (69 NHL and 16 ALL) subjects were enrolled in Phase 1, with 61 in Part A (45 NHL and 16 ALL) and 24 in Part B (all NHL). Among the enrolled subjects, 82 received CTX110 infusion and 3 (2 in Part A and 1 in Part B, all NHL) did not.

[redacted]

[redacted]

# 5. DEFINITIONS AND GENERAL METHODOLOGY

## 5.1. Definitions of Analysis Sets

### 5.1.1. Enrolled Set

All subjects who signed the informed consent form (ICF), completed screening and met all eligibility criteria. The subjects in Enrolled Set will be classified according to the assigned CTX110 dose level and regimen.

### 5.1.2. DLT Evaluable Set (DES)

All subjects enrolled in dose escalation (Part A) who received CTX110 infusion and completed the DLT evaluation period or discontinued earlier after experiencing a DLT. The DLT evaluation period will begin with the first CTX110 infusion and last for 28 days. The subjects in DES will be classified according to the received dose level of initial CTX110 infusion in each cohort. The DES was used for determination of RPBD.

### 5.1.3. Safety Analysis Set (SAS)

All subjects who received CTX110 infusion. The subjects in SAS will be classified according to the received CTX110 dose level and regimen in each cohort. The SAS will be the primary analysis set for characterization of CTX110 safety profile.

### 5.1.4. Full Analysis Set (FAS)

All subjects who received CTX110 infusion. The subjects in FAS will be classified according to the assigned CTX110 dose level and regimen in each cohort. The FAS will be the primary analysis set for assessment of CTX110 efficacy.

## 5.2. General Methodology

Disposition, demographic and baseline characteristics, exposure, efficacy, safety, and PK data will be summarized.

Categorical data will be summarized by frequency distributions (number and percentages of subjects) and continuous data will be summarized by descriptive statistics (number of subjects [n], mean, standard deviation, median, minimum, and maximum). All data will be provided in by-subject listings.

The data of the two indications (NHL and ALL) will be summarized separately, and reported in two sets of table/listing/figure (TLF) output. Within each indication, data of each cohort will be analyzed separately without pooling across cohorts except that legacy Cohort F will be included in Cohort A for analysis (details about Cohort F in Section 3.1.1 Section 3.1.1 of the SAP).

In each cohort, the CTX110 dose level and regimen will be used to classify subjects, unless otherwise specified. In particular, for Cohort A, 4 subjects in Phase 1 Part A were assigned CTX110 dose level 4 with Day 1 and Day 35 2-infusion regimen (denoted by DL4*), and the subjects in Phase 1 Part B were assigned DL4* as well, therefore, the data of the 4 subjects in Phase 1 Part A will be combined with those of Phase 1 Part B for analyses. For the subjects in

Phase 1 Part A other than the 4 Cohort A subjects with DL4*, data will be summarized by initial dose level of CTX110 infusion for each cohort. The 8 subjects in the discontinued Phase 2 had the same disease (NHL) and were assigned DL4*, and the data of these 8 subjects will be combined with those of Phase 1 Cohort A DL4* subjects for analyses except for efficacy.

All analyses and summary tables will have the analysis set sample size (i.e., number of subjects) for each dose level and regimen of CTX110 and overall in the column/row heading as applicable.

All percentages, except for 100%, will be rounded to 1 decimal place. All mean and median values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places. Minimum and maximum values will be presented to the same number of decimal places as raw data.

## 5.3. Randomization and Blinding

This is an open-label study with no randomization at enrollment. All subjects are assigned to CTX110.

## 5.4. Baseline values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, and prior to, the start of any study treatment, including LD chemotherapy, CTX110, and daratumumab (Cohort C). Values collected at unscheduled visits prior to the start of LD chemotherapy or daratumumab will be included in the calculation of baseline values.

## 5.5. Method of Pooling Data

All data from all sites will be pooled. Study center or treatment-by-center interactions will not be included in any statistical analysis.

The data of Phase 1 Cohort A subjects who were assigned CTX110 dose level 4 with Day 1 and Day 35, two-infusion regimen (denoted by DL4*), and those of Phase 2 subjects (all assigned to DL4*) will be pooled for analyses except for efficacy.

## 5.6. Handling of Missing Values

No imputation will be performed for missing values except for missing date (detailed in Section 9.1 of the SAP). For missing end date that could indicate an ongoing event (e.g., AEs and concomitant medication), the by-subject listings will include an indicator for ongoing status. Other missing data will be noted as missing.

No imputation will be performed for missing dates for by-subject listings. However, the imputation will be implemented for summary tabulations, when applicable.

## 5.7. Relative Day since CTX110 Infusion

The date of initial CTX110 infusion will be considered relative day 1, and the day before the date of initial CTX110 infusion will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after the date of initial CTX110 infusion:

Date of Assessment – Date of initial CTX110 infusion + 1.

For days before the date of initial CTX10 infusion:

Date of Assessment – Date of initial CTX110 infusion.

## 5.8. Visit Windows

Whenever possible, the study assessments should occur on the scheduled visit day or specified time. Minor deviations from the scheduled visit day are allowed to accommodate subjects' schedules (See protocol Section 7 for schedule of assessments). 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. More details can be found in Section 7.2 of the study protocol. All disease assessments will be included for both summary and listings. For safety analyses, the assessments occurring at the scheduled visits are the primary assessments used for the statistical analyses. Other assessments falling outside the planned window will be included in worst grade derivation, but not in descriptive statistics. They will be included in data listings.

## 5.9. Follow-up Durations

Potential follow-up duration among all subjects treated with CTX110 will be calculated as the time interval from the first infusion of CTX110 to data cutoff date.

Actual follow-up duration among all subjects treated with CTX110 will be calculated as the time interval from the first infusion of CTX110 to the death date or last known alive date. The last known alive date is the last non-imputed date of any subject record in the study database.

# 6. STATISTICAL ANALYSES

## 6.1. Subject Disposition

Summaries by CTX110 dose level and regimen as well as overall for each cohort will be provided. The number and percentage of subjects in the following analysis sets/subsets will be summarized:

- Enrolled Set
- DLT Evaluable Set (DES)
- Safety Analysis Set (SAS)
- Full Analysis Set (FAS)

The percentage will be calculated based on the number of enrolled subjects in each dose level/regimen or overall within each cohort.

The number and percentage of subjects in each disposition category below will be summarized with the number in the Safety Analysis Set (SAS) as the denominator:

- On study
- Completed study
- Discontinued from the study
  - Reasons for discontinuations

Subject disposition data will be listed including phase/part, cohort, CTX110 dose level and regimen, enrollment date, date of initial CTX110 infusion, status in study, actual follow-up, study completion/discontinuation date, and reasons for discontinuation as applicable.

Screen failures will be listed. For re-screened subjects, enrollment status is based on the outcome of the last screening event.

## 6.2. Major Protocol Deviations

By-subject listing for major protocol deviations will be provided.

## 6.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using the FAS. Individual by-subject listings will be provided to support the summary tables.

### 6.3.1. Demographics

Age (years), baseline height (cm), baseline weight (kg), baseline body mass index (BMI), and body surface area (BSA) will be summarized with descriptive statistics. Age category (<65 versus ≥65 years), sex, ethnicity, and race will be summarized by frequency tabulations (count, percentage).

Body mass index will be calculated as: BMI ($kg/m^2$) = (weight in kg) / (height in m)$^2$.

Body surface area will be calculated as: BSA ($m^2$) = square root of ((weight in kg) x (height in cm)/3600).

### 6.3.2. Baseline Disease Characteristics

The following baseline characteristics of Non-Hodgkin lymphoma (NHL) will be summarized:

- Relapse versus refractory based on the response to the last line of prior anti-cancer therapy for NHL
- Primary refractory, defined as no CR to the first line for prior therapy, or high-risk relapse, defined as relapse within 12 months since the start of the first line.
- Bulky disease (yes, no): the presence of a single target lesion with largest diameter being ≥7.5 cm per CT scan
- Tumor size as measured by sum of products of perpendicular diameters (SPD) of target lesions (summary statistics, and categorical summary of <50 $cm^2$ versus ≥50 $cm^2$)
- Extranodal disease (Yes, No)
- Subtype of Non-Hodgkin lymphoma:
  - 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
  - Grade 3b follicular lymphoma
  - Richter's transformation of chronic lymphocytic leukemia
  - Primary mediastinal large B-cell lymphoma (PMBCL)
- Lugano Stage of NHL (I-IV) at study entry
- ECOG Performance Status (PS) at baseline (0-5)

The following baseline characteristics of Acute Lymphoblastic Leukemia (ALL) will be summarized:

- Lymphoblasts count:
  - <5%
  - ≥5%
- Disease status: Relapse, Refractory
- Disease description at diagnosis: De novo ALL, Therapy related ALL
- BCR/ABL1 Fusion (Philadelphia Chromosome) Status: Positive, Negative
- High risk: Positive, Negative

- Other extramedullary disease presence: Yes, No
- ECOG Performance Status (PS) at baseline (0-5)

## 6.4. Prior, concomitant, and post-treatment medications/procedures

Prior, concomitant, and post-treatment medications/procedures will be coded using the World Health Organization (WHO) Drug Dictionary. Missing date imputation rules are included in Section 9.1.

### 6.4.1. Prior Anti-Cancer Therapy

All prior anti-cancer therapy information will be listed with the following to be summarized:

Prior chemo/immunotherapy

Total number of lines of therapy (summary statistics, and categorically by 2, ≥3)

Category of prior chemo/immunotherapy

Prior radiation therapy

- Number and percentage of subjects who had prior radiation therapy

Prior stem cell transplant

- Number and percentage of subjects who had prior stem cell transplant, either autologous (for NHL) or allogeneic (for ALL)

### 6.4.2. Medical History

Medical Dictionary for Regulatory Affairs (MedDRA) will be used to code medical history, including system organ class (SOC) and preferred term (PT).

Medical history will be listed in a by-subject listing.

### 6.4.3. Concomitant Medications or Procedures

Concomitant medications or procedures refer to those that were ongoing at the start of lymphodepletion (LD) chemotherapy or that were initiated after the start of LD chemotherapy. All concurrent therapies, including prescription and nonprescription medication, are 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 are collected: IV immunoglobulins, vaccinations, [redacted], immunosuppressants (including steroids), and any investigational agents.

Concomitant medications will be coded per WHO Drug Dictionary, and will be listed. Concomitant procedures will be coded per MedDRA, and will be listed.

## 6.5. Extent of Exposure and Compliance to Study Treatment

Study treatment includes lymphodepletion (LD) chemotherapy, CTX110 CAR T cell therapy, and daratumumab (Cohort C only). The first and the second course of CTX110 treatment will be summarized separately. Subjects will be classified based on the CTX110 dose and regimen of the respective course of treatment.

### 6.5.1. Lymphodepletion Regimen

Lymphodepletion (LD) regimen includes LD chemotherapy (fludarabine + cyclophosphamide) for all cohorts, and additional daratumumab for cohort C (Section 3.1.1 of the SAP).

Summary of exposure to LD chemotherapy (fludarabine + cyclophosphamide) will include actual daily dose normalized by body surface area ($mg/m^2$). Summary of exposure to daratumumab (Cohort C only) will include actual average dose normalized by body weight (mg/kg per dose). Categorical summary by total number of doses (1, 2, 3, etc) will also be provided.

The number and percentage of subjects with the following types of dose modification will also be summarized:

- Dose adjusted, by reason for dose decreased.
- Dose interrupted, by reason for dose interrupted.

The summaries will be provided for fludarabine, cyclophosphamide, and daratumumab (Cohort C only) separately. By-subject listings of the exposure to LD regimen and dose modifications will be provided.

### 6.5.2. CTX110 CAR-T cell therapy

Summary of exposure to CTX110 CAR T cell therapy will include the following cell types for each course of treatment:

- Total CAR+ T cells.

For the first course of treatment, categorical summary by total number of infusions (1, 2) will be provided. Average exposure to CTX110 (in number of CAR+ T cells) for the first infusion and total exposure to CTX110 during the first course will be summarized. The number and percentage of subjects who were administered the second course of treatment will be provided. For the second course of treatment, the exposure to CTX110 will be summarized as well.

By-subject listings of the exposure to CTX110 CAR+ T cell therapy will be provided.

## 6.6. Efficacy Analyses

The efficacy of CTX110 for NHL will be assessed per 2014 Lugano response criteria for lymphoma (Cheson et al., 2014) (Appendix 14.1 in the study protocol), and that for ALL will be assessed per B-Cell Acute Lymphoblastic Leukemia Response Evaluation Criteria adapted from 2021 National Comprehensive Cancer Network (NCCN) guidelines for treatment of acute lymphoblastic leukemia Version 2 (NCCN Guidelines ALL, v2, 2021) (Appendix 14.6 in the study protocol). For subjects who received a second course of CTX110 treatment, disease

assessments before and after the second course will be combined in efficacy analysis. Response assessments after post-CTX110 anti-cancer therapy will be excluded for the derivation of best overall response (BOR). In the analyses of the time-to-event endpoints with censoring, subjects who received post-CTX110 anti-cancer therapy will be censored at the last adequate disease assessment before the start of post-CTX110 anti-cancer therapy. Efficacy analyses will be performed based on local efficacy assessments by investigators.

The efficacy analysis results will essentially be presented by CTX110 dose level and regimen for each cohort using FAS. The Phase 1 Cohort A (including legacy Cohort F) subjects who were assigned CTX110 dose level 4 with Day 1 and Day 35 two-infusion regimen (DL4*) in Part A and Part B will be combined for summary. For Phase 1 Cohort D with ALL subjects, the Subcohorts D1 and D2 will be summarized separately. No efficacy analysis will be performed for Phase 2.

The analyses on the efficacy endpoints as described below will be performed, with the results reported in respective summary tables.

### 6.6.1. Response Rate type endpoints

Objective response/remission rate (ORR)

ORR will be based on best overall response (BOR) for each subject. BOR is defined as the best response that a subject achieved during the study.

For NHL subjects (Cohorts A, B and C) assessed per Lugano response criteria, the best overall response for each subject is determined by the following hierarchical order (from best to worst): complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). The ORR refers to the proportion of subjects with BOR of CR or PR as determined by local investigator.

For ALL subjects (Cohort D, including Subcohorts D1 and D2) assessed per B-Cell ALL Response Evaluation Criteria adapted from 2021 NCCN guidelines for treatment of ALL Version 2, the best overall response for each subject is determined by the following hierarchical order (from best to worst): complete remission (CR), complete remission with incomplete blood count recovery (CRi), blast-free hypoplastic or aplastic bone marrow, partial response (PR), non-response, progressive disease (PD)/relapsed disease. The ORR refers to the proportion of subjects with BOR of CR or CRi as determined by local investigator.

Complete response/remission rate (CRR)

CRR is defined as the rate of complete response/remission (CR) per protocol-specified response criteria for NHL and ALL, respectively.

[redacted] rate for ALL

For ALL subjects, the [redacted] rate is defined as the proportion of subjects who ever achieved [redacted] status among CR responders.

The response rate type of endpoints will be summarized by number and percentage of subjects along with the 2-sided exact 95% CI constructed using Clopper-Pearson method.

In addition, a swimlane plot to depict the response assessments following CTX110 infusion for individual subjects will be provided for Cohort A DL4* subjects. And a waterfall plot to depict the best percent changes in SPD of target lesions from baseline for individual subjects will be provided for Cohort A DL4* subjects.

### 6.6.2. Time-to-event Endpoints with Censoring

The following time-to-event endpoints with censoring will be analyzed for NHL subjects (Cohorts A, B and C):

Duration of response (DOR)

Among subjects who achieved objective response (CR or PR), DOR will be calculated as the longest time interval from an occurrence of objective response (OR) to the first disease progression or death following the OR, whichever occurred first.

Progression-free survival (PFS)

PFS will be calculated from the first CTX110 infusion to the first progression or death, whichever occurred first.

Overall survival (OS)

OS is defined as the time from the first CTX110 infusion to the death due to any cause.

The time-to-event endpoints will be censored if subjects withdraw, drop out, are lost to follow-up, or roll over to long-term follow-up study before documentation of the events (progression/death). Censoring rules are detailed in the following table.

**Table 3: Censoring rules for time-to-event endpoints**

| Endpoint | Situation | Date of censoring |
|---|---|---|
| DOR, PFS | No post-baseline assessment, no death | Date of CTX110 infusion |
| | No PD or death | Date of last adequate response assessment |
| | Post-CTX110 alternative anti-cancer therapy started prior to PD or death | Date of last adequate response assessment prior to the post-CTX110 alternative anti-cancer therapy |
| | 2 or more consecutive missing scheduled response assessments from last response assessment prior to PD or death | Date of last adequate response assessment prior to missed scheduled assessments |
| OS | No death | Last known alive date |

Note: Adequate response assessment refers to a response assessment other than "Unknown". If there is no adequate assessment prior to the start of post-CTX110 [redacted]/long gap, use the CTX110 infusion date as the censoring date.

For OS, subjects who are alive at the analysis cut-off date will be censored at the last known alive date. The last known alive date is the last non-imputed date of any subject record in the study database. This date may be the last visit date or last contact date that the subject is known

to be alive. Subjects who only have a baseline record will be censored at the date of first CTX110 infusion.

The time-to-event endpoints with censoring will be analyzed using Kaplan-Meier (KM) methods. The median of each endpoint with 2-sided 95% CI, as well as KM estimates of probability to remain in the duration at key time points (e.g., 6, 12, and 24 months) will be provided. Kaplan-Meier curves will also be presented if there is sufficient data.

## 6.7. Safety and Tolerability

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 AE reporting requirements for different time periods in the study (Section 8.7 in the study protocol).

The safety analyses will be based on the safety data during the overall treatment-emergent period (since the first CTX110 infusion to the end of follow-up) in the safety analysis set, i.e., all the subjects who received CTX110 infusion.

Safety data will be summarized by CTX110 dose level and regimen as well as overall for each cohort. All safety data collected since the time of informed consent will be listed.

Adverse events (AEs) will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) at the time of analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, except for CRS, which will be graded according to the ASTCT consensus recommendations (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). More details on AE severity grading can be found in Section 8.4 of the study protocol.

### 6.7.1. Dose-Limiting Toxicities

DLTs are defined in the study protocol (Section 4.1.4.2). DLTs will be flagged in the by-subject listing of AE.

### 6.7.2. Adverse Events

Summaries of AEs will focus on treatment-emergent AEs (TEAEs), which refer to AEs that start or worsen on or after the first CTX110 infusion. The Safety Analysis Set will be used as the analysis set for CTX110 TEAEs. The incidence of CTX110 TEAEs will be summarized according to MedDRA by system organ class (SOC) and/or preferred term (PT), CTCAE grade, and relation to study treatment. If a subject experiences multiple AEs under the same PT within a SOC, the subject will be counted only once for that PT within that SOC. If a subject experiences the same AE more than once with different grades, the event with the highest grade will be tabulated in by-grade tables.

The following tables summarizing the incidence of TEAEs during the treatment-emergent period in the Safety Analysis Set will be generated:

- Overall summary of TEAEs
- All TEAEs by SOC and PT
- AESI by grade
- All TEAEs by PT, in order of frequency among overall subjects
- Grade 3 or higher TEAEs by SOC and PT
- TEAEs related to CTX110 by SOC and PT
- Grade 3 or higher TEAEs related to CTX110 by SOC and PT
- Serious AEs (SAEs) by SOC and PT
- Serious AEs (SAEs) related to CTX110 by SOC and PT
- AEs leading to death by SOC and PT

For overall summary of TEAEs, the following categories will be included:

- Subjects with any TEAE
- Subjects with grade ≥3 TEAE
- Subjects with TEAE related to LD chemotherapy
- Subjects with TEAE related to CTX110
- Subjects with grade ≥3 TEAE related to LD chemotherapy
- Subjects with grade ≥3 TEAE related to CTX110
- Subjects with AESI
- Subjects with Grade ≥3 AESI
- Subjects with serious TEAE
- Subjects with serious TEAE related to LD chemotherapy
- Subjects with serious TEAE related to CTX110
- Subjects with TEAE leading to LD chemotherapy interrupted
- Subjects with TEAE leading to LD chemotherapy dose adjusted
- Subjects with TEAE leading to discontinuation from study
- Subjects with TEAE leading to death
- Subjects with DLT

By-subject AE listings for all AEs will be provided for all subjects in Enrolled Set.

### 6.7.3. Adverse Events of Special Interest

An adverse event of special interest (AESI) refers to an AE of scientific and medical concern specific to the sponsor's product for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate (Section 8.3 in the study protocol). Number and percentage of subjects who experienced AESI will be summarized for each grade (1-5), using Safety Analysis Set by CTX110 dose level and regimen as well as overall for each cohort.

The following AESI categories will be presented:

- CTX110 infusion reactions
- Grade ≥3 infections
- Tumor lysis syndrome
- Cytokine release syndrome (CRS)
- Immune effector cell–associated neurotoxicity syndrome (ICANS)
- B-cell aplasia
- Hemophagocytic lymphohistiocytosis (HLH)
- Hypogammaglobulinemia
- Graft versus host disease (GvHD)
- Secondary malignancy
- Uncontrolled T cell proliferation
- Any new hematological or autoimmune disorder that the investigator determines is possibly related or related to CTX110.

### 6.7.4. Death

Summary of all-cause mortality in Safety Analysis Set will be provided, with categories of time of death (≤30, ≤60, ≤90 and >90 days) relative to the last CTX110 infusion. Death listing will also be provided for all subjects in Enrolled Set. The death date and the relative day since the last CTX110 infusion will be displayed if applicable.

### 6.7.5. Clinical Laboratory Evaluations

For laboratory tests covered by the CTCAE version 5.0, laboratory results will be graded accordingly. A Grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges. If a lab value is reported using a non-numeric qualifier (e.g., less than [<] a certain value, or greater than [>] a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

The following summary tables for selected lab abnormalities, including hematopoietic cytopenia, will be provided:

- Table with categorical summary of subjects with lab abnormalities based on CTCAE v5.0 toxicity criteria, focused on the lab parameters of hematology, chemistry, and coagulation. Summaries of all grade and grade >=3 lab abnormalities will be provided.
- Table with categorical summary of subjects with Grade 3 or 4 hematopoietic cytopenias (including lymphopenia, neutropenia, leukopenia, anemia, and thrombocytopenia) following the first course of treatment. The incidence rates of Grade 3 or 4 cytopenias at selected timepoints (D28, M2 and M3) will be summarized. Grading of cytopenias will be derived using lab results in absolute lymphocytes, absolute neutrophils, leukocytes, hemoglobin or platelet count according to CTCAE v5.0.

In addition to the summary table, the listings of hematology, serum chemistry and coagulation laboratory data with the corresponding CTCAE grades relative to the laboratory normal ranges will be provided for all subjects in Safety Analysis Set. The listing of grade 3 or 4 hematopoietic cytopenia lab abnormalities in Safety Analysis Set will be provided as well.

## 6.8. Pharmacokinetics (PK) Analyses

Whole blood PK samples are collected according to the schedule of assessments as specified in the study protocol (Tables 16 and 17 in Section 7). PK of CTX110 is primarily evaluated using a droplet digital PCR (ddPCR) assay that measures copies of anti-CD19 CAR construct per µg genomic DNA (gDNA) isolated from peripheral blood samples collected over time.

The PK analyses will focus on the disposition of CTX110 over the first 28 days since the first infusion. For subjects who received a second infusion of CTX110, the PK data of the second infusion will be analyzed separately from that of the first infusion. For each subject, the CTX110 level at a specific scheduled timepoint will be the average of all the reportable replicates from the raw PK data. For qualitative results in the raw PK data, “Detected” will be imputed as 8.75 copies/µg, which is halfway between the limit of detection (LOD, 5.8 copies/µg) and the lower limit of quantification (LLOQ, 11.7 copies/µg); and “Not Detected” will be imputed as 2.9 copies/µg, which is ½ LOD. Missing PK data will be omitted in these analyses.

CTX110 levels in whole blood at each scheduled timepoint will be summarized using descriptive statistics by CTX110 dose level based on Full Analysis Set (FAS). A line plot depicting the individual-subject CTX110 levels over the time course of D1-D28 since the first CTX110 infusion will be provided for Cohort A subjects (Phase 1 and 2) whose initial CTX110 dose levels are DL3, DL3.5 and DL4. Additionally the population-wise median level for DL4 will be indicated in the plot.

In addition, observed PK parameters will be derived based on CTX110 concentration data. The PK parameters to be derived and included in PK analysis are the following:

- Peak expansion ($C_{max}$): The maximum CTX110 concentration after the initial nadir post CTX110 infusion. If all the timepoints after the initial nadir have CTX110 levels below the LOD (i.e., there is no CTX110 expansion), the $C_{max}$ of the subject will be imputed as ½ LOD (i.e., 2.9 copies/µg).
- Time to peak expansion ($T_{max}$): The elapsed time (in days) from each CTX110 infusion to peak expansion. If there is no CTX110 expansion, no $T_{max}$ will be derived for the subject.
- Time of last detectable CTX110 ($T_{last}$): The elapsed time (in days) from CTX110 infusion to last observed detectable concentration of CTX110 in peripheral blood, where "detectable" means the average value of all reportable replicates is above LOD ($\geq$ 5.8 copies/µg). If there is no CTX110 expansion, no $T_{last}$ will be derived for the subject.

The observed PK parameters will be summarized using descriptive statistics by CTX110 dose level based on Full Analysis Set (FAS). A dot plot depicting the individual-subject values of $C_{max}$ following the first CTX110 infusion grouped by CTX110 dose level will be provided for Cohort A subjects (Phase 1 and 2) whose initial CTX110 dose levels are DL3, DL3.5 and DL4. The median value of $C_{max}$ for the dose level group will be indicated in the dot plot.

All raw PK measurements and observed PK parameters for individual subjects will be listed.

# 7. COMPUTER SOFTWARE

SAS Version 9.3 or later will be used to perform the analyses and produce the specified tables, listings, and figures.

# 8. REFERENCES

Cheson, B.D., Fisher, R.I., Barrington, S.F., Cavalli, F., Schwartz, L.H., et al. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol *32*, 3059-3068.

Harris, A.C., Young, R., Devine, S., Hogan, W.J., Ayuk, F., et al. (2016). International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant *22*, 4-10.

Lee, D.W., Santomasso, B.D., Locke, F.L., Ghobadi, A., Turtle, C.J., et al. (2019). ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant *25*, 625-638.

NCCN.org (2021). NCCN Guidelines, Acute Lymphoblastic Leukemia, Version 2.2021. July 19, 2021.

# 9. APPENDIX

## 9.1. Imputation Methods for Missing Data in Dates

### 9.1.1. Missing/Partial Dates in Adverse Events

**Missing/Partial Start Date:**

1. *Missing day only*
   - If the month and year are the same as that of Day1 (Date of 1st dose of CTX110), Day1 will be assigned
   - If the month and year are before that of Day1, the last day of the month will be assigned
   - If the month and year are after that of Day1, the first day of the month will be assigned
2. *Missing day and month*
   - If the year is the same as that of Day1, Day1 will be assigned
   - If the year is before that of Day1, December 31 will be assigned
   - If the year is after that of Day1, January 1st will be assigned
3. *Missing day, month, and year*
   - Day1 will be assigned

If the stop date is non-missing and the imputed start date is after the stop date, the stop date will be used as the start date.

**Missing/Partial Stop Date:**

1. *Missing day only*
   - The last day of the month will be assigned as the missing day.
2. *Missing day and month*
   - December 31 will be assigned to the missing fields.
3. *Missing day, month and year*
   - If the event is resolved but the stop date is complete missing, then the end of study date or data cut off data whichever is earlier will be assigned.

If the start date is non-missing and the imputed stop date is before the start date, the start date will be used as stop date. If the death date is available and the imputed stop date is after the death date, the death date will be used.

### 9.1.2. Missing/Partial Dates in Prior Anti-cancer Therapy, Prior HSCT, Prior Radiation Therapy

**Missing/Partial Start Date:**

1. *Missing day only*
    - 15th of the month or enrollment date – 15 days, whichever earlier
2. *Missing day and month*
    - 15th of June, if that is after enrollment date – 15 days then assigned it to January 1st
3. *Missing day, month, and year*
    - No imputation will be applied

If the stop date is non-missing and the imputed start date is after the stop date, the stop date will be used as the start date.

**Missing/Partial Stop Date:**

1. *Missing day only*
    - 15th of the month or enrollment date – 15 days, whichever earlier
2. *Missing day and month*
    - 15th of June, if that is after enrollment date – 15 days then assigned it to January 1st
3. *Missing day, month, and year*
    - No imputation will be applied

If the start date is non-missing and the imputed stop date is before the start date, the start date will be used as stop date.

## 9.2. Summary of Changes

Key changes from v1 to v2

- Global: The v2 of the SAP added ALL indication on top of NHL, so it covers both indications.
- Section 2 Study Objectives:
  - Added the objectives for Phase 2 on top of those for Phase 1.
- Section 3.1 Overall Study Design:
  - Added Phase 2 on top of Phase 1.
  - Updated Part B to be expansion part of Phase 1, and removed the hierarchical testing strategy.
- Section 3.2 Study Measures and Endpoints:
  - Consolidated primary and secondary efficacy endpoints, so there is no distinction between primary and secondary efficacy endpoints.
  - Changed the central efficacy data to local ones for efficacy analyses.
  - Removed efficacy endpoints DOCB, TFFS and TTR.
  - Added [redacted] rate for ALL.
- Section 3.3 Sample Size Estimation
  - Combined Part A and Part B in Phase 1, and simplified Part B.
  - Added Phase 2 and indicated that the enrollment for Phase 2 was discontinued.
- Section 4 [redacted]
  - Simplified the [redacted], and clarified that the [redacted] as planned for Phase 2 in the protocol would not be performed given the discontinuation of enrollment in Phase 2.
- Section 5.1 Definitions of Analysis Sets:
  - Removed Treated Set.
- Deleted Section 5.2 (Definitions of primary population and bulky-refractory population) and Section 5.3 (Definition for course of treatment) in v1.
- Section 5.2 General Methodology (Section 5.4 in v1)
  - Added the language that the DL4* subjects from Phas1 Part A and Part B will be combined for all analyses, and the 8 subjects in the discontinued Phase 2 will be combined with the DL4* subjects in Phase 1 for analyses except for efficacy.
- Section 5.5 Method of Pooling Data
  - Added the language that the data of Phase 1 Cohort A DL4* and those of Phase 2 subjects will be pooled for analyses except for efficacy.

- Section 6.1 Subject Disposition
  - Removed the summary of Treated Set.
- Section 6.2 Major Protocol Deviations
  - Removed the summary of critical and major protocol deviations. Only keep the listing.
- Section 6.3.1 Demographics
  - Removed the age category of <75 versus >75 years.
- Section 6.3.2 Baseline Disease Characteristics
  - Removed the categorical summary based on time from the start of the first line of prior anti-cancer therapy for NHL to CTX110 initial infusion (<=7 months versus >7 months).
  - Removed the categorical summary of N1 and N2 subsets.
  - Updated the cutoff of largest diameter for bulky disease to be >=7.5cm instead of >=10cm.
  - Added the baseline characteristics of ALL.
- Deleted Section 6.4.4 (Post-CTX110 anti-cancer therapy) in v1.
- Deleted Section 6.5.2 (Daratumumab) in v1.
- Section 6.5.2 CTX110 CAR-T cell therapy (Section 6.5.3 in v1)
  - Removed the summary of cell types "Total nucleated cells" and "CAR+ T cells per body weight".
- Section 6.6 Efficacy Analyses
  - Added the description of response assessment for ALL.
  - Changed the central efficacy data to local ones for efficacy analyses.
  - Added the language about the combination of DL4* subjects from Phase 1 Part A and Part B for efficacy analyses, and clarified that no efficacy analysis will be performed for Phase 2.
- Section 6.6.1 Response Rate type endpoints (Primary Efficacy Endpoint in v1)
  - Removed the hierarchical testing of null hypothesis.
  - Removed the supportive analyses on ORR.
  - Added the derivation of ORR and CRR for ALL on top of that for NHL.
  - Added the description of [redacted] for ALL.
- Section 6.6.2 Time-to-event Endpoints with Censoring
  - Removed DOCB, TFFS and TTR.

  - Moved the table of censoring rule (Table 3) to this section.
- Deleted Section 6.6.3 (Subgroup Analyses) in v1.
- Deleted Section 6.6.4 (Efficacy Analyses of Dose Escalation).
- Section 6.7 Safety and Tolerability
  - Simplified the safety analyses by removing the distinction between the primary and the secondary analysis of safety data, and replacing them with one set of analyses based on data during the overall treatment-emergent period.
  - Removed the description and the figure of primary and secondary safety analysis periods.
- Section 6.7.1 Dose-Limiting Toxicities
  - Simplified the DLT analysis by removing the summary of DLTs and only flagging DLTs in the by-subject listing of AE.
- Section 6.7.2 Adverse Events
  - Simplified the AE analyses by summarizing the incidence of TEAEs during the treatment-emergent period in the Safety Analysis Set.
- Section 6.7.5 Clinical Laboratory Evaluations
  - Removed the summaries of hematology and serum chemistry lab parameters.
  - Added the summary table of lab abnormalities based on CTCAE toxicity criteria.
  - Updated the summary table of time to resolution among patients with prolonged Grade 3 or 4 cytopenias to be the one with categorical summary of subjects with Grade 3 or 4 cytopenias at selected timepoints.
  - Removed the summary tables with descriptive statistics for ECG parameters.
- Added Section 6.8 for PK analyses.

Signature Page

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