NOVARTIS

Clinical Development

CTL019/Tisagenlecleucel/Kymriah®

CCTL019BUS03 / NCT04225676

A phase II, open label, multi-center trial to determine the efficacy and safety of tisagenlecleucel re-infusion in Pediatric and Adolescent Young Adult (AYA) patients with acute lymphoblastic leukemia experiencing loss of B cell aplasia

Statistical Analysis Plan (SAP) Amendment 2

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10-Mar-2020	Prior to DBL	Creation of final version	Not applicable - First version	Not applicable
14-Apr-2021	Prior to DBL	Alignment with most recent protocol (protocol v1.0) and minor edits (including fixing typos); Alignment with recent guidance from regulatory authorities; Alignment with recent COVID-19 guidance; Removal of redundant sections	Amendment 1	All
		Clarification that descriptive statistics of analysis sets will be provided		Section 2.2 Analysis sets
		Addition of a summary of study follow-up; Update of study follow-up categories		Section 2.3.1 Patient disposition
		Addition of a demographics summary table presented by age stratification		Section 2.3.2 Demographics
		Addition of a summary table of patients exposed to tisagenlecleucel by sex and age category; Clarification of body weight		Section 2.4.1 Study treatment / compliance
		Addition of definition for fludarabine based lymphodepleting chemotherapy		Section 2.4.2 Additional treatments
		Addition of definition for time since CTL019 re-infusion to HSCT; Addition of summary and listing of post re-infusion anti-neoplastic therapies		Section 2.4.3 Prior and concomitant medication and therapies
		Addition of new subgroups of interest		Section 2.5 Subgroup analyses
		Addition of details on the analysis of the primary endpoint by time point		Section 2.6.2 Statistical hypothesis, model and method of analysis
		Clarification that best overall disease response is not confirmed		Section 2.8.1.1 Overall remission rate

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Removal of EFS subgroup categorization		Section 2.8.2.2 Event free survival
		Addition of details on presenting MRD assessment summary table; Clarification of overall rather than best disease response		Section 2.8.4 Other efficacy assessments
		Aligned descriptive AE summaries with other CTL studies; Addition of summary of AEs by timing of onset		Section 2.9.1 Adverse Events
		Addition of summary of deaths by timing of onset		Section 2.9.1.1 Deaths
		Addition of summary of AESIs by timing of onset		Section 2.9.1.2 Adverse events of special interest / grouping of AEs
		Addition of details on CRS summaries; Addition of time to first CRS onset analysis; Addition of time to resolution of first CRS onset analysis		Section 2.9.1.3 Cytokine release syndrome
		Removal of change from baseline to worst post re-infusion value summary table and addition of patient lab profile listings; Addition of summaries of hematopoietic cytopenias not resolved by day 28		Section 2.9.2 Laboratory data
		Addition of details on B-cell and T-cell; Clarification of time to B-cell recovery analysis		Section 2.9.2.1.1 B-cell and T-cell level
		Addition of details on Healthcare Resource Utilization summaries		Section 2.9.3.2 Other safety assessments
		Addition of visit for tisagenelecluecel concentattion measured by qPCR; Addition of value of LLOQ		Section 2.10 Pharmacokinetic endpoints
		Addition of details on CTCAE grading for laboratory values		Section 5.3 Laboratory parameter derivations

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Addition of details on laboratory parameter imputations		Section 5.3.1 Imputation rules
29-Nov-2021	Prior to DBL	Trial closeout early due to feasibility/very low rate of enrollment; SAP has been updated to align with short/lean closeout CSR. Only listing will be presented. B-cell aplasia definition updated.	Amendment 2	All Section 2.6

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List of abbreviations

AE	Adverse event
ALL	Acute Lymphoblastic Leukemia
ATC	Anatomical Therapeutic Classification
AYA	Adolescent Young Adult
BMI	Body Mass Index
CAR	Chimeric Antigen Receptor
CD	Cluster of Differentiation
CI	Confidence Interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CR	Complete Remission
CRi	Complete Remission with incomplete blood count recovery
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
ENS	Enrolled Set
FAS	Full Analysis Set
FPFV	First Patient First Visit
IRC	Independent Review Committee
LD	Lymphodepleting
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantication
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRD	Minimal Residual Disease
ORR	Overall Remission Rate
OS	Overall Survival
PB	Peripheral Blood
PD	Pharmacodynamics
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
PT	Preferred Term
qPCR	Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Set
SCT	Stem Cell Transplant
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

TFLs	Tables, Figures, Listings
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes the primary statistical analysis according to the statistical methodology of the clinical trial protocol CTL019BUS03 (version 1.0, release date 23-Jun-2020) along with any additional analyses, specifications, or deviations from the protocol. This SAP may be used as a first draft of Section 9.7 (Statistical methods planned in the protocol and determination of sample size) and Appendix 16.1.9 (Documentation of statistical methods) of the Clinical Study Report (CSR).

Determination of the sample size is specified in Section 3.

In the original SAP, it was planned that the primary analysis would be conducted at the end of the study when all patients who were re-infused with tisagenlecleucel had completed a 12-month study period. For this analysis, all primary, secondary, [redacted] objectives were to be addressed including all variables outlined up to Month 12 and all available safety data. Separate SAP documentation was to be created for any ad-hoc interim analyses required for publication.

However, this study terminated early due a very low rate of enrollment, which made it no longer feasible to continue with the trial; which meant there was insufficient data to perform the planned statistical analyses so study data will be listed only. This SAP amendment was issued after the decision to terminate the study; therefore, the changes to planned analyses are reflected in this document (see Section 4).

This document is written in the future tense. It will be reviewed and updated (including conversion to past tense) for entry into the CSR after the analysis has taken place.

1.1 Study design

This is a phase II, open label, multi-center trial which aims to determine the efficacy and safety of tisagenlecleucel re-infusion in pediatric and adolescent young adult with acute lymphoblastic leukemia (ALL) experiencing loss of B-cell aplasia. The patient population for this study will be comprised of patients up to and including 25 years of age who have been previously infused with commercial tisagenlecleucel and have an additional dose of commercial tisagenlecleucel available and prescribed to them by a physician in the course of medical practice. Additionally, these patients must have loss of B-cell aplasia defined as:

- Peripheral blood (PB) absolute B lymphocyte count $\geq$ 50/µL, OR
- Peripheral blood B lymphocyte $\geq$ 10% of the total lymphocytes.

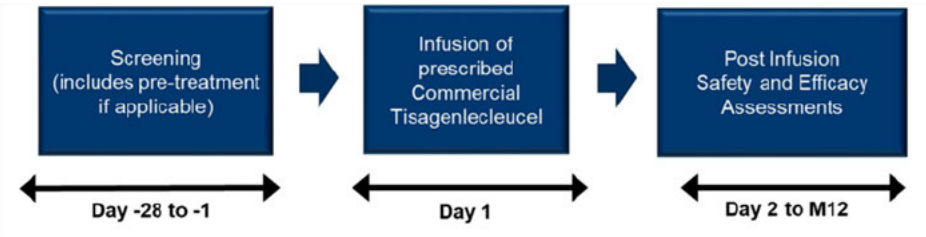
The study will have the following sequential phases for all patients as depicted in Figure 1-1: Screening and Treatment (including tisagenlecleucel re-infusion and assessment period)

After tisagenlecleucel re-infusion, efficacy will be assessed at Day 28, Month 3, 6, and 12. The primary analysis time point will be Month 12. Safety will be assessed throughout the study. The end of the study is defined as the last patient's last visit (LPLV), which is the last patient's Month 12 visit, or the time of premature withdrawal. A final CSR will be produced once all patients complete or discontinue from the study.

A post-study follow-up for lentiviral vector safety will continue under the Center for International Blood and Marrow Transplant Research (CIBMTR) cellular therapy registry for 15 years post re-infusion per health authority guidelines.

No formal interim analysis is planned for this study.

Figure 1-1 Study Design



1.2 Study objectives and endpoints

Objectives and related endpoints are provided in Table 1-1.

Table 1-1 Study objectives and endpoints

Objectives	Endpoints
Primary Objective	**Endpoint for primary objective**
• Evaluate the incidence of B-cell aplasia after re-infusion of tisagenlecleucel	• Proportion of patients who establish B-cell aplasia within 12 months of re-infusion, as measured by circulating B lymphocytes (< 50/µL) in the peripheral blood.
Secondary Objectives	**Endpoints for secondary objectives**
• Evaluate the efficacy of re-infusion of tisagenlecleucel for loss of B-cell aplasia as measured by Overall Remission Rate (ORR) 12 months after tisagenlecleucel re-infusion, which includes complete remission (CR) and CR with incomplete blood count recovery (CRi) as determined by investigator assessment for pALL patients	• Proportion of patients with ORR (= CR + CRi) per Investigator assessment in pALL patients during 12 months post re-infusion.
• Evaluate Event Free Survival (EFS)	• EFS, i.e. the time from date of tisagenlecleucel re-infusion to the earliest of relapse, treatment failure or death
• Evaluate Overall Survival (OS)	• OS, i.e. the time from date of tisagenlecleucel re-infusion to the date of death due to any reason

Objectives	Endpoints
• Evaluate the safety of tisagenlecleucel re-infusion therapy	• Safety parameters including adverse events (AEs) and laboratory abnormalities

[redacted]

2 Statistical methods

2.1 Data analysis general information

This study will be conducted under the sponsorship of Novartis.

The analysis outlined in this document will be performed by Novartis or a designated contract research organization (CRO) (if applicable). SAS® version 9.4 or higher will be used for generating tables, figures, and listings (TFLs). It is planned that the data from all participating centers will be used.

Data will be listed for all patients with respect to demographic and baseline characteristics, efficacy, and safety observations and measurements.

All data will be listed by center, patient number and one treatment arm of the tisagenlecleucel (tisagenlecleucel is as defined in Section 2.1.1.1), unless stated otherwise.

2.1.1 General definitions

2.1.1.1 Tisagenlecleucel re-infusion

A second dose of commercial tisagenlecleucel is not considered study treatment because it is released commercially to the treating physician when it is prescribed in the course of medical practice. The doses available for re-infusion were previously manufactured for each individual patient as commercial product and a physician can request an additional dose for commercial release at any time, prior to product expiration and subject to availability.

2.1.1.2 Date of re-infusion of tisagenlecleucel

The date of re-infusion of tisagenlecleucel is defined as the date when a non-zero dose of tisagenlecleucel was administered and recorded on the "Dosage Administration Record - IV - Tisagenlecleucel T-Cell Infusion (Second Infusion)" electronic Case Report Form (eCRF). A single re-infusion is planned. Note that re-infusion refers to the **second** infusion of tisagenlecleucel. This study will follow the patient journey post re-infusion.

2.1.1.3 Date of infusion of tisagenlecleucel

Note that prior to study enrollment into this re-infusion study, patients will have a date for their first tisagenlecleucel infusion. The date of first infusion is recorded on the "Dosage Administration Record - IV - Tisagenlecleucel T-Cell Infusion (First Infusion)" eCRF.

2.1.1.4 Date of first administration of lymphodepleting chemotherapy

The date of first administration of lymphodepleting chemotherapy is defined as the first date when a non-zero dose of lymphodepleting chemotherapy was administered and recorded on the "Bridging or Lymphodepleting Chemotherapy-Medication" eCRF for the indication "Lymphodepleting chemotherapy".

2.1.1.5 Date of first administration of bridging therapy

The date of first administration of bridging therapy is defined as the first date when a non-zero dose of bridging therapy was administered and recorded on the "Bridging or Lymphodepleting Chemotherapy-Medication" eCRF for the indication "Bridging therapy".

2.1.1.6 Date of first treatment

For patients who received lymphodepleting chemotherapy and/or bridging therapy prior to re-infusion, the date of first treatment is the date of first administration of lymphodepleting chemotherapy or bridging therapy. For patients who did not receive lymphodepleting chemotherapy or bridging therapy, the date of first treatment is the date of re-infusion of tisagenlecleucel.

2.1.1.7 Study day

The study day will be calculated as the difference between the date of the assessment and the date of re-infusion of tisagenlecleucel (defined as **Study Day 1**) plus 1 day for assessments on or after the date of re-infusion. Duration of an event will be calculated as:

- Duration of event = (Event end date – Event start date) + 1 (in days)

For assessments before the date of re-infusion, the study day will be calculated as the difference between the date of the assessment and **Study Day 1** *(Note: if an event happens before Study Day 1 then the study day will be negative).*

For patients who do not receive tisagenlecleucel in this study, their study days will not be calculated.

For the partial date study day will not be calculated.

The study days will be displayed in all relevant data listings.

2.1.1.8 Baseline assessments

Not applicable.

2.1.1.9 Last contact date

Not applicable.

2.1.1.10 Time-to-event

Not applicable.

2.1.1.11 Percent change from baseline

Not applicable.

2.2 Analysis sets

Screened Set: The Screened Set comprises all patients who have signed informed consent/assent and been screened in the study.

Enrolled Set: The Enrolled Set (ENS) comprises all patients who are enrolled in the study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria and the patients' additional non-expired dose of tisagenlecleucel has been confirmed available.

Full Analysis Set: The FAS consists of all patients who have received re-infusion of tisagenlecleucel.

Safety Set: The Safety Set consists of all patients who have received re-infusion of tisagenlecleucel.

2.3 Patient disposition, demographics and other baseline characteristics

All baseline disease characteristics and demographics will be listed from Enrolled Set, unless stated otherwise.

No inferential tests for differences in background and demographic characteristics will be performed.

2.3.1 Patient disposition

The patient disposition for each phase will be listed for the Screened Set for all patients who entered the study. Patients who have entered any study phase but have discontinued from the study will be listed as appropriate along with the primary reason for discontinuation.

2.3.2 Demographics

The following demographic data will be listed:

Note: Dependent on when the COVID-19 pandemic may end versus when patients are enrolled in this study, the listing may be given by pandemic impact.

- Age at Screening (years)
  Age at Screening stratification category (<10 years, ≥10 to < 18 years, ≥18 years)
- Sex (Male, Female, Unknown, Undifferentiated)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)
  - Defined as: (weight in kg) / (height in meters)^2
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)

- Karnofsky/Lansky performance status (100, 90, 80, 70, 60, 60, <50)

2.3.3 Baseline characteristics

2.3.3.1 Primary disease history

The following primary disease history will be listed:

Note: Dependent on when the COVID-19 pandemic may end versus when patients are enrolled in this study, the listing may be given by pandemic impact.

- Age at initial diagnosis (years)
- WBC at initial diagnosis ($\geq 50\times10^9$ cells/L, $< 50\times10^9$ cells/L)
- Date of initial diagnosis of ALL (years)
- Date of first tisagenlecleucel infusion (months)
- Date of loss of B-cell aplasia following first tisagenlecleucel infusion (months)
  Note: Date of loss of B-cell aplasia is equivalent to date of study enrollment.

2.3.3.2 ALL characteristics

The following ALL disease characteristics at Baseline will be listed

- Evidence of extramedullary involvement (Yes, No)
- CD19 status (Positive, Negative, Not Done, Unknown)
- Overall minimal residual disease (MRD) status (Positive, Negative, Not Done, Unknown)
- MRD biomarker analyte and associated phenotype result (%)

2.3.3.3 Medical history

Medical history and ongoing conditions at Baseline will be listed.

Note: If there are COVID-19 infected patients in this study, listing of medical history will be provided first by all patients of interest, then by COVID-19 infected patients and non-COVID-19 infected patients.

Medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology version 24.1 or higher. The primary SOCs will be presented in alphabetical order. Preferred terms will be sorted by decreasing proportion and alphabetical order.

2.3.3.4 ALL prognostic factors

The qualitative ALL prognostic factors as captured on the "Prognostic factors" eCRF and will be listed.

- Age (≤ 12 years, > 12 years, Unknown)
- Elevated lactate dehydrogenase (LDH) > upper limit of normal (Yes, No, Unknown)
- Disease stage III/IV (Yes, No, Unknown)
- Extranodal involvement (Yes, No, Unknown)

2.3.3.5 Prior anti-neoplastic therapies

All prior anti-neoplastic therapies including medications for hematological disease and radiotherapy will be listed.

2.3.3.6 Protocol deviation summaries

A listing of protocol deviations will be produced including the accompanying deviation code.

In addition, all COVID-19 related protocol deviations will also be listed.

2.3.4 Unscheduled visits

All data collected at unscheduled visits will be listed.

2.3.5 Others

All other data collected at baseline will be listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Tisagenlecleucel re-infusion

Total viable cells re-infused (in cells), total CAR positive viable T-cells re-infused (in cells/kg) and total CAR positive viable T-cells re-infused (in cells) will be listed for each patient using Safety Set.

The approved dose range for this trial is: 0.2 to 5.0×10^6 CAR positive viable T-cells / kg for patients' $\leq$ 50 kg body weight or 0.1 to 2.5×10^8 (i.e. 10 to 250×10^6) CAR positive viable T-cells for patients > 50 kg body weight. Patients will be categorized as above, within or above the prescribed dose range by body weight stratum (i.e. $\leq$ 50 kg and > 50 kg).

Note: Body weight refers to the body weight collected on the "Vital Signs" eCRF at the Study Day 1 assessment (i.e. re-infusion assessment).

2.4.2 Additional treatments

Additional treatments data will be listed using the Enrolled Set.

Lymphodepleting chemotherapy received after enrollment but prior to re-infusion with tisagenlecleucel will be listed. Types of lymphodepleting chemotherapies received (fludarabine based lymphodepleting therapy, non-fludarabine based lymphodepleting therapy and no lymphodepleting therapy) will also be listed by patient.

Note: Fludarabine based lymphodepleting chemotherapy refers to fludarabine or fludarabine phosphate.

Any instances of bridging therapy will also be listed.

2.4.3 Prior and concomitant medications and therapies

Prior (pre re-infusion) and concomitant (post re-infusion) medications will be listed by the reported term and PT according to the WHO Drug Reference List dictionary (version 202109 GLOBAL B3 or higher).

Significant non-drug therapies post re-infusion including stem cell transplants (SCTs) will be listed.

The number of patients requiring anti-cytokine medications for the management of Cytokine Release Syndrome (CRS) as well as the dosage will be listed by patient using Enrolled Set.

In addition, all post re-infusion anti-neoplastic therapies including medications for hematological disease and radiotherapy will be listed using Safety Set.

2.5 Subgroups of interest

Not applicable.

2.6 Analysis of the primary objective

The primary objective of the study is to evaluate the efficacy of re-infusion of tisagenlecleucel for restoring B-cell aplasia as measured by the incidence of B-cell aplasia within 12 months following tisagenlecleucel re-infusion.

Where **loss of B-cell aplasia** (i.e. B-cell recovery) is defined as:

- PB absolute B lymphocyte count ≥50/µL, OR
- Peripheral blood B lymphocyte ≥10% of the total lymphocytes

And where **B-cell aplasia** is defined as:

- PB absolute B lymphocyte count <50/µL

The primary analysis of the study was to be performed after all patients had completed the 12-month follow-up period or discontinued earlier. However, this study terminated early due a very low rate of enrollment, and only 5 out of a planned 54 patients were enrolled; the low sample size provides insufficient data to perform the planned statistical analyses (see Section 4). Therefore, the available study data will be listed only for the primary objective using Full Analysis Set.

2.6.1 Primary endpoint

The primary endpoint for this study is defined as the proportion of patients who restore B-cell aplasia (as defined in Section 2.6) within 12 months following re-infusion with tisagenlecleucel as measured by circulating B-lymphocytes (<50/µL) in PB. B-cell aplasia data will be listed by patient using Full Analysis Set.

2.6.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis was to be performed by testing the following hypothesis:

- H_0: $p \leq 0.10$ vs. H_A: $p > 0.10$

The estimated proportion $\hat{p}$ of patients who restore B-cell aplasia within 12 months following re-infusion with tisagenlecleucel will be presented together with an exact 95% Clopper-Pearson confidence interval (CI).

The null hypothesis was to be rejected if the lower limit of the 95% CI was greater than 0.10, demonstrating improvement after re-infusion. The estimated number of patients who restore B-cell aplasia required to reject the null hypothesis (H_0) is 10 (See Appendix Section 5.4).

The primary analysis will not be conducted as planned due to not enough patients enrolled for a meaningful analysis, based on early termination of the study as described above and in Section 4. Data for the primary objective will be listed only.

2.6.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.6.4 Supportive analyses

Not applicable.

2.6.4.1 Sensitivity analyses

Not applicable.

2.6.4.2 Subgroup analyses

Not applicable.

2.7 Analysis of the key secondary objective

There are no key secondary objectives for this study.

2.8 Analysis of secondary efficacy objectives

Note: The secondary efficacy analysis will not be performed as there is an inadequate number of patients in the study.

2.8.1 Secondary endpoints

Note: The secondary efficacy analysis will not be performed as there is an inadequate number of patients in the study.

2.8.1.1 Overall remission rate

Note: The secondary efficacy analysis will not be performed as there is an inadequate number of patients in the study.

2.9 Safety analyses

2.9.1 Adverse events

All AEs and SAEs data (including data from the pre re-infusion period) will be listed using Screened Set.

Treatment-emergent AEs (TEAEs) are defined as AEs that started or worsened after tisagenlecleucel re-infusion.

In addition, for the legal requirements of clinicaltrials.gov and EudraCT, two required tables on TEAEs which are not SAEs with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to tisagenlecleucel will be provided by primary SOC and PT using Safety Set.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same primary SOC and PT:

- A single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.
- More than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE. For occurrence, the presence of at least one SAE/SAE suspected to be related to tisagenlecleucel/non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.9.1.1 Deaths

Death data will be listed using the Screened Set.

2.9.1.2 Adverse events of special interest / grouping of adverse events

Not applicable.

2.9.1.3 Cytokine release syndrome

Cytokine release syndrome data will be listed using the Safety Set.

2.9.2 Laboratory data

Laboratory data will be listed for all patients in the Enrolled Set. Results will be graded by the low/normal/high classifications based on laboratory normal ranges.

2.9.3 Other safety data

Other safety data will be listed using the Enrolled Set.

2.9.3.1 Vital signs

Vital signs data will be listed.

2.9.3.2 Other safety assessments

Karnofsky/Lansky performance scores (100, 90, 80, 70, 60, 60, <50) will be listed.

All other safety data will be listed.

2.10 Pharmacokinetic endpoints

For all pharmacokinetic (PK) analyses, the Enrolled Set will be used, unless stated otherwise.

No inferential tests for PK analyses will be performed.

Tisagenlecleucel concentrations in peripheral blood will be measured by qPCR and listed by treatment, subject, and visit (D1 pre-dose, D28, M3 and M12) from Full Analysis Set. Concentrations below 10 copies/reaction (LLOQ) will be treated as zero. All unplanned PK results will be listed.

2.12 Interim analysis

No formal interim analysis was planned for this study. Interim analyses could have been performed half-yearly following study start as required for publication purposes; however, no interim analyses were actually required due to early termination of the study.

3 Sample size calculation

This study is an exploratory study to determine the safety and efficacy of tisagenlecleucel re-infusion with an early loss of B-cell aplasia. The primary efficacy variable is the proportion of patients who restore B-cell aplasia (as defined in Section 2.6) within 12 months following re-infusion.

Sample size was based on an exact test for single proportion to test the null hypothesis H_0: $p \leq 0.10$, where p is the proportion of patients recovering B-cell aplasia during 12 months. If the true rate $p \geq 0.25$, then with a one sided alpha level of 2.5% and at least 80% power, a minimum of 49 evaluable patients will be required for the study. Considering a drop-out rate of 10%, a total of approximately 54 patients will be enrolled into the study.

4 Change to protocol specified analyses

The HESTER Trial has enrolled 5 patients over the course of one year. Given this rate of enrollment, the ability to enroll the planned number of patients within a reasonable time period is no longer feasible. Therefore, after careful consideration, it was decided to close the trial. Data is not adequate to perform statistical analysis. All study data will be listed.

The decision to close the study is not based on any issues related to safety.

Primary endpoint updated by removing text “presence of CTL019 cells by qPCR in the peripheral blood” from B-cell aplasia definition.

5 Appendix

5.1 Imputation rules

Not applicable.

5.2 AEs coding/grading

Reporting of AEs will be based on MedDRA version 24.1 or higher and the CTCAE version 4.03 or higher. The grading of CRS will be based on study protocol specific grading scales. For the analysis purpose, the latest version of MedDRA available at analysis cut-off date will be used for reporting activity.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

Not applicable.

5.5 Visit windows

Not applicable.

5.6 Rule of exclusion criteria of analysis sets

Not applicable.

6 References

[Novartis (2020) COVID-19 CTT Guidance_Developing Clinical Study Reports (CSRs) for Studies Conducted During the COVID-19 Pandemic_V4.0 15-Sep-2021.]