NOVARTIS

Clinical Development

CTL019/Tisagenlecleucel/Kymriah®

CCTL019B2001X / NCT03123939

Phase IIIb study for relapsed/refractory pediatric/young adult acute lymphoblastic leukemia patients to be treated with CTL019

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)
16-Jan-2016	Prior to DBL	Creation of final version	Not applicable - First version	Not applicable
10-Aug-2020	Prior to DBL	Updated to align with most recent protocol (protocol v04) and eCRF Rearranged some sections to align with latest SAP template Replaced SCT with HSCT for clarification Removed the section for Event Free Survival category as is not of interest for the CSR Updated the list of abbreviations Clarified that overall remission rate is CR and CRi Clarified which efficacy analyses will have a per protocol analysis Clarified which efficacy analyses would have a subgroup analysis	Amendment 1	All
		Updated secondary endpoints based on data collected in this study		Section 1.2 Study objectives and endpoints
		Clarified the secondary endpoints		Section 4 Change to protocol specified analyses
		Added details on how to derive Date of first administration of briding therapy		Section 2.1.1.2 Study day and other key dates
		Removed reference to pharmacokinetics from the cellular kinetics analysis set		Section 2.2 Analysis sets
		Added an additional major protocol deviation		

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		based on other CTL studies		
		Removed the safety subgroup analyses as not required for CSR and converted the efficacy subgroup analyses to subgroup analyses		Section 2.2.1 Subgroups of interest
		Removed subgroup analyses which were not of clinical interest or had insufficient patients to warrant a subgroup analysis		
		Updated the age categories for the age subgroup to align with ICH guidelines		
		Updated the baseline bone marrow tumor burden definition as MRD absolute results are not collected in this study		
		Included summary of patients enrolled by country and site		Section 2.3.1 Patient disposition
		Added age subgroup category to fulfil regulatory reporting guidelines		Section 2.3.2 Demographics and other baseline characteristics
		Added descriptive summaries in relation to blinatumomab and inotuzumab		Section 2.3.2.3 Prior anti-neoplastic therapy
		Added details for adverse event outputs required to fulfil safety disclosure requirements		Section 2.5.2.1 Adverse events
		Added definition for safety reporting period		
		[redacted]		Section 2.7.2.4 Duration of remission

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		[redacted] Removed competing risks analysis as the competing risk event is not present in the study data		
		Clarified which are the subgroups of interest		Section 2.7.2.9 Impact of baseline tumor burden on response
		Clarified that quality of response refers to proportion of patients with MRD negative disease response		Section 2.7.2.10 Quality of response using MRD assessments
		Added 2-sided exact (Clopper Pearson) 95% CI to be presented along with proportion of MRD negative patients		
		Removed reference to IRC assessment (not applicable for this study)		Section 2.8.4 Cytokine release syndrome and anti-cytokine therapies
		Removed Kaplan Meier analyses as not required for the CSR		
		Removed reference to selected clinical outcomes being summarized descriptively by CTL019 product characteristics (not of interest to CTT)		Section 2.8.5 Apheresis product processing and CTL019 product characteristics
		Clarified the apheresis product processing and CTL019 product characteristics planned analyses		
		Clarified that other safety data be listed only		Section 2.8.6 Other safety data
		Updated list of cellular kinetic parameters		Section 2.9.1 Cellular kinetics

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		following discussion with study PK analyst		
		Added details for T-cell summaries Defined B-cell recovery		Section 2.12.1 B-cell and T-cell levels
		Updated derivation for follow-up time for DOR and RFS		Section 5.2 Time-to-event analyses
		Added this section to provide derivation for baseline bone marrow tumor burden and renumbered subsequent sections		Section 5.4 Baseline bone marrow tumor burden
04-DEC-2020	Prior to DBL	Clarified that the age subgroup is referring to age at screening	Amendment 2	General
		Updated minimum dose reference to align with the protocol		Section 2.2 Analysis sets
		Clarified the age subgroup categories; Updated race and ethnicity categories to align with CDISC standards; Updated weight for CTL019 manufacturing categories		Section 2.3.2 Demographics and other baseline characteristics
		Added details on descriptive summaries for post CTL019 infusion HSCT		Section 2.4.2 Prior, concomitant and post therapies
		Study discontination is not collected on the AE CRF so removed reference to summary tables for AEs leading to study discontinuation		Section 2.5.2.1 Adverse events
		Clarified that median values and ranges are only of interest for Tlast		Section 2.9.1 Cellular kinetics
		Table 5-2: Added time window details for MRD assessment in bone		Section 5 Appendix

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		marrow (flow cytometry; qPCR); Added time windows for lab assessments (Table 5-4) and renumbered subsequent tables; Table 5-9: Updated PD numbering to align with latest DRP		

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List of abbreviations

AE	Adverse event
ALL	Acute Lymphoblastic Leukemia
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
CART19	CD19-directed Chimeric Antigen Receptor T-cell
CDBL	Clinical Database Lock
CI	Confidence Interval
CK	Cellular Kinetics
CKAS	Cellular Kinetics Analysis Set
CNS	Central Nervous System
CR	Complete Remission
CRi	Complete Remission with Incomplete Blood Recovery
CRO	Clinical Research Organization
CRS	Cytokine Release Syndrome
CSF	Cerebral Spinal Fluid
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DOR	Duration of response
eCRF	Electronic Case Report Form
EFS	Event-free Survival
ENS	Enrolled Set
FAS	Full Analysis Set
HSCT	Hematopoietic Stem Cell Transplant
ICU	Intensive Care Unit
KM	Kaplan-Meier
LTFU	Long-term Follow-up
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MLL	Mixed-lineage Leukemia
MRD	Minimal Residual Disease
OS	Overall Survival
PPS	Per-Protocol Set
PRO	Patient-reported Outcome
PT	Preferred Term
qPCR	Quantitative Polymerase Chain Reaction
RCL	Replication Competent Lentivirus
RFS	Relapse-free Survival
TEAE	Treatment-emergent Adverse Event
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan

SD	Standard Deviation
SOC	System Organ Class
TFLs	Tables, Figures, Listings
VSV-g	Vesicular Stomatitis Virus, Glycoprotein
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the primary statistical analysis according to the detailed statistical methodologies planned for the clinical trial protocol CTL019B2001X (version 04, release date 06-Aug-2019) along with any additional analyses, specifications, or deviations from the protocol planned before unmasking of the data. 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). 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 single-arm, multi-center, Phase IIIb study will provide pediatric/young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) the opportunity to be treated with CTL019 after the closure of enrollment to the Novartis single-arm Phase II clinical trial (i.e. Study CTL019B2202). The main purpose of this study is to assess the safety of CTL019 for up to 12 months after the CTL019 infusion.

This study will have the following sequential phases for all patients as depicted in Figure 1-1:

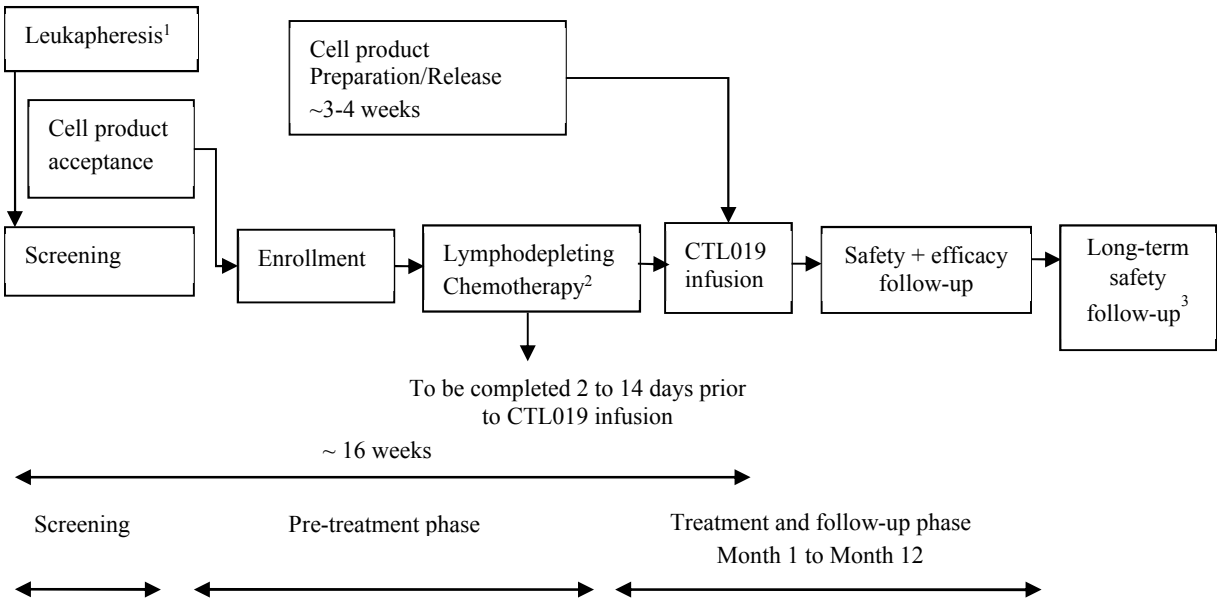
- Screening phase
- Pre-treatment (cell product preparation and lymphodepleting chemotherapy)
- Treatment and follow-up
- Long-term follow-up (LTFU) under a separate protocol (i.e. CCTL019A2205B)

Each enrolled patient will be followed for up to 12 months after the single CTL019 infusion, after which time they will be transitioned into the LTFU protocol.

After the single CTL019 infusion on Day 1, efficacy will be assessed at Month 1, 3, 6, 9 and 12 or until patient relapse.

No formal interim analysis is planned. The safety data will be reviewed periodically. A final clinical CSR will be produced once all patients complete or prematurely discontinue the study.

Figure 1-1 Study design



1 Performed prior to study entry.
2 As indicated per protocol.
3 Long-term safety follow-up conducted per health authority guidance under a separate protocol.

1.2 Study objectives and endpoints

The list of study objectives and corresponding endpoints as presented in the study protocol are specified in Table 1-1.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
• Evaluate the safety of CTL019 therapy.	• Type, frequency and severity of adverse events (AEs) and laboratory abnormalities.
Secondary	
• Evaluate the efficacy of CTL019 therapy as measured by overall remission rate (ORR), which includes complete remission (CR) and CR with incomplete blood count recovery (CRi).	• Percentage of patients who achieve CR or CRi during the 6 months after CTL019 infusion.
• Evaluate the percentage of patients who achieve CR or CRi at Month 6 without hematopoietic stem cell transplantation (HSCT) between CTL019 infusion and Month 6 response assessment.	• Percentage of patients who achieve CR or CRi at Month 6 without HSCT between CTL019 infusion and Month 6 response assessment.
• Evaluate the percentage of patients who achieve CR or CRi and then proceed to HSCT while in remission before Month 6 response assessment.	• Percentage of patients who achieve CR or CRi and then proceed to HSCT while in remission prior to Month 6 response assessment. • In addition, all patients that proceed to HSCT after CTL019 infusion will be described.
• Evaluate the duration of remission (DOR).	• DOR, i.e. the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to ALL. • Site of involvement of subsequent relapse will be summarized.
• Evaluate the relapse-free survival (RFS).	• RFS, i.e. the time from achievement of CR or CRi whichever occurs first to relapse or death due to any cause during CR or CRi.
• Evaluate the event-free survival (EFS).	• EFS, i.e. the time from date of CTL019 infusion to the earliest of death, relapse or treatment failure.
• Evaluate the overall survival (OS).	• OS, i.e. the time from date of CTL019 infusion to the date of death due to any reason.
• Evaluate the response at Day 28 ± 4 days.	• Proportion of patients attaining CR or CRi at Day 28 ± 4 days post CTL019 infusion.
• Evaluate the impact of baseline tumor burden on response.	• Descriptive summary of response at Day 28 ± 4 days post CTL019 infusion as a function of baseline tumor burden (tumor load) (i.e. by the subgroup baseline bone marrow tumor burden).
• Evaluate the quality of response using minimal residual disease (MRD) assessments before treatment and at Day 28 ± 4 days after treatment and before HSCT by local assessment (flow cytometry or quantitative polymerase chain reaction [qPCR]).	• Descriptive summary of MRD qualitative result (positive/negative) before treatment and at Day 28 ± 4 days after treatment and before HSCT by local assessment (flow cytometry or qPCR).

Objective	Endpoint
• Describe the prevalence and incidence of immunogenicity of antibodies against CTL019.	• Prevalence and incidence of immunogenicity and anti-CTL019 assay titers.
• Characterize the *in vivo* cellular kinetic profile (levels, persistence, trafficking) of CTL019 cells in the blood.	• Maximum concentration (C_{max}), time to peak concentration (T_{max}), AUCs and other relevant kinetic parameters of CTL019 in the blood. • Persistence of CTL019 in the blood.
• Evaluate the relationship between exposure to CTL019 with cytokine release syndrome (CRS) grades.	• Relationship of C_{max} and $AUC_{0\text{-}28d}$ of CTL019 in the blood with CRS grade.

2 Statistical methods

2.1 Data analysis general information

This study will be conducted under the sponsorship of Novartis.

The data analysis will be performed by Novartis or designated clinical research organization (CRO) if applicable.

The data from all participating centers will be combined and analyzed using statistical analysis software (SAS®, Cary, NC, USA) version 9.4 or higher.

The continuous variables will be summarized using standard descriptive statistics including mean, standard deviation (SD), median, minimum and maximum. The following number of decimal places will be used: mean, median to 1 more decimal place than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data.

The categorical outcome variables will be summarized by means of contingency tables by one treatment group for non-missing data; a row (category) denoted “missing” will be included in count tabulations if a non-zero count of missing values is present. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. If a count of zero is obtained, the zero count and percentage will still be displayed.

The primary analysis time point is the end of the follow-up phase at Week 52.

All tables and listings will be presented by one treatment arm (i.e. CTL019 infusion). All data will be listed by center and patient number, unless stated otherwise.

2.1.1 General definitions

The following section contains general definitions and naming conventions which will be used in this and all other statistical and programming modules (tables, figures and listings [TFLs] mock shells and programming data specifications).

2.1.1.1 Study drug and study treatments

Study drug is defined as CTL019 transduced cells, also known as CD19-directed chimeric antigen receptor T-cell (CART19) or tisagenlecleucel. This will henceforth be referred to as

CTL019 infusion. Study treatment includes not only CTL019 infusion but also lymphodepleting chemotherapy.

2.1.1.2 Study day and other key dates

2.1.1.2.1 Study follow-up phase

The study includes a treatment (CTL019 infusion) and follow-up period (of 1 year after infusion of patients) to monitor the disease responses (blood, bone marrow and extramedullary disease etc.) and safety. The end of the 1-year period will mark the end of study. The date of study completion or last contact date with the patient in the event of premature discontinuation will be considered the end of the follow-up phase.

2.1.1.2.2 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 chemotherapy is administered and recorded on the "Concomitant Antineoplastic Therapy" electronic Case Report Form (eCRF) for the indication "Lymphodepleting".

2.1.1.2.3 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".

2.1.1.2.4 Date of CTL019 infusion

The date of CTL019 infusion is defined as the date when a non-zero dose of CTL019 transduced cells was administered and recorded on the "Dosage administration record" eCRF.

2.1.1.2.5 Date of first study treatment

For patients who received lymphodepleting chemotherapy and/or bridging therapy, the date of first study 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 study treatment is the date of CTL019 infusion.

2.1.1.2.6 Study day

The study day will be calculated as the difference between the date of the assessment and the date of first CTL019 infusion (defined as Study day 1) plus 1 day for assessments on or after the date of CTL019 infusion. The 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 first CTL019 infusion, the study day will be calculated as the difference between the date of the assessment and the date of first CTL019 infusion (Study day 1). Note: If an event happens before the first day of CTL019 infusion then the study day will be negative.

For patients who did not receive CTL019 infusion, their study days will not be calculated.

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

2.1.1.3 Baseline assessments

For baseline disease evaluations, the most current assessments (bone marrow, blood count, cerebral spinal fluid (CSF), physical examination, etc.) on or prior to the date of enrollment will be used as the baseline characteristics.

For the bone marrow aspirate results, the highest blasts value will be considered, and the corresponding assessment date will be used as reference for other assessments.

For safety evaluations (i.e. laboratory and vital signs), the last available assessment before CTL019 infusion will be taken as the "baseline" value.

If patients have no value as defined above, the baseline results will be missing.

2.1.1.4 Post-baseline assessments

All assessments obtained after CTL019 infusion are referred to as post-baseline assessments.

2.1.1.5 Last contact date

The last contact date will be used for censoring of patients in the analysis of OS. For patients not known to have died as of the analysis cut-off date, the last contact date should be derived as the latest date on or before the data cut-off date from the dates listed in the first column of Table 2-1. For each of the sources specific conditions listed in the second column of Table 2-1 have to be fulfilled to ensure that there is true contact with the patient. No additional dates are allowed to be used, e.g. dates coming from concomitant medications, patient reported outcomes (PROs), etc.

Table 2-1 Last contact date data sources

Source data	Conditions
Last date patient was known to be alive from the Survival Follow-up eCRF page	No condition
Start/end dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/end dates from dosage administration record	Non-missing dose
Any specific efficacy assessment date if available	Evaluation is not missing
Laboratory/cellular kinetic (CK) collection dates	Sample collection with non-missing value
Vital signs date	At least one non-missing parameter value
Performance status date	Non-missing performance status
Start/end dates of AE	Non-missing verbatim term

Note: completely imputed dates will not be used to derive the last contact date. Partial date imputation is allowed to be used for the event (death) and censoring date only if it is taken from the Survival Follow-up eCRF page (see Section 5.6.6 for details).

2.1.1.6 Lost to follow-up

For response related time to event analysis (i.e. DOR, RFS and EFS), patients will be considered as lost to follow-up if they discontinued the study due to loss to follow-up.

2.2 Analysis sets

The analysis sets to be used are defined below. The definition of the analysis sets are not dependent on the age of the patient. All TFLs will be presented by one treatment arm of CTL019.

Screened Set

The Screened Set will comprise all patients who have signed the informed consent/assent and are screened in the study.

Enrolled Set

The Enrolled Set (ENS) will comprise 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 patient's leukapheresis product is received and accepted by the manufacturing facility.

Full Analysis Set

The Full Analysis Set (FAS) will comprise all enrolled patients who have received an infusion of CTL019.

Safety Set

The Safety Set (SAF) will comprise all patients who received an infusion of CTL019. By this definition, the FAS and the SAF will be the same for this study.

Cellular Kinetic Analysis Set

The CK analysis set (CKAS) will consist of patients in the FAS who have at least 1 sample providing evaluable CK data. The CKAS will be used for summaries (tables and figures) and listings of CK data.

Note: Patients will be removed from the estimation of certain CK parameters on an individual basis depending on the number of available samples. These patients will be identified at the time of the analyses.

Per-protocol Set

The Per-Protocol Set (PPS) will consist of a subset of patients in the FAS who are compliant with major requirements of the study protocol.

Major protocol deviations leading to exclusion from the PPS may include:

- No diagnosis of ALL at baseline;
- Prior therapy does not match with CCTL019B2001X protocol requirements in terms of number and types of previous therapy regimens;
- Missing or incomplete documentation of disease;

- CTL019 T-cells were infused to patients without fulfilling either of the following 2 conditions: (A) meeting all approved manufacturing release criteria; (B) released through exceptional release.

In addition, patients who receive a dose less than the minimum target dose of 0.2×10^6 (for patients ≤ 50 kg) or 0.1×10^8 (i.e. 10×10^6) (for patients > 50 kg) CTL019 transduced viable T-cells per kg of body weight will also be excluded.

The detailed exclusion criteria of PPS will be determined prior to clinical database lock (CDBL) (see Section 5.9 for details).

Screening disposition information will be summarized based on the Screened Set. The ENS will be used to summarize pre-treatment disposition data and to list whether patients received CTL019 or not. The primary objective will be evaluated using the SAF. All other safety analysis will be performed on the SAF. The FAS will be used as the efficacy analysis set. The CKAS will be used for all CK analysis.

2.2.1 Subgroups of interest

Subgroup analyses will only be performed if there are at least 5 patients present in each subgroup level. Some grouping of classes will be considered if there are too few patients in some subgroups.

The subgroup analyses will be performed on the following based on the patient's baseline status:

- Age at screening: ≥ 28 days to < 2 years, ≥ 2 years to < 12 years, ≥ 12 years to < 18 years, ≥ 18 to < 65 years

  Note: Due to the small number of patients in the subgroup level ≥ 28 days to < 2 years, the first 2 subgroup levels will be combined into 1 subgroup level: < 12 years.
- Baseline bone marrow tumor burden: Low (defined as morphologic result is < 50%), High (defined as morphologic result is ≥ 50%)

Efficacy analyses in subgroups will generally be purely exploratory and intended to explore the intrinsic consistency of any treatment effects found overall.

Subgroup analyses of the ORR will be performed on the FAS by presenting the point estimates in the subgroup with the exact 95% confidence intervals (CIs).

2.3 Patient disposition, demographics and other baseline characteristics

All demographic and other baseline data will be listed by patient and summarized descriptively for the FAS, unless otherwise specified.

2.3.1 Patient disposition

Patient disposition will be summarized for the following: screening phase for the Screened Set, pre-treatment phase for the ENS, treatment and follow-up phase for the FAS. The treatment and follow-up phase disposition data will also be presented by the subgroup age at screening (defined in Section 2.2.1).

The patient disposition for each phase will be summarized for all patients who entered that phase. The number and percentage of patients in each of the categories as listed for "End of Phase Disposition" eCRF pages will be tabulated and listed along with their reason for premature discontinuation.

For the screening phase, the clinical eligibility criteria that were not met by patients will also be tabulated. In addition, the number and percentage of patients who enrolled in the long term follow-up study will be summarized.

Patients who have entered any study phase but have not completed/discontinued will be listed as appropriate.

In addition, for the legal requirements of clinicaltrials.gov and EudraCT, the number and percentage of patients enrolled in each country and site will be provided.

2.3.2 Demographics and other baseline characteristics

Descriptive statistics will be presented overall and by the subgroup age at screening (defined in Section 2.2.1) for the following continuous demographic and other baseline characteristics variables:

- Age (years)
- Age at initial diagnosis of ALL (years)
- Weight for CTL019 manufacturing (kg)
- Time since initial diagnosis of ALL (years)
  - Defined as: (date of screening – date of initial diagnosis of ALL) / 365.25
- Time since initial diagnosis of ALL to first relapse/progression (months)
  - Defined as: (date of first relapse/progression - date of initial diagnosis of ALL + 1) / 30.4375
- Time since most recent relapse/progression to CTL019 infusion (months)
  - Defined as: (date of CTL019 infusion – date of most recent relapse/progression + 1) / 30.4375

The number and percentage of patients in each category of the following categorical variables will be presented:

- Age (< 10 years, ≥ 10 to <18 years, ≥ 18 years)
- Age at initial diagnosis of ALL (< 10 years, ≥ 10 years)
- Sex (male, female)
- Weight for CTL019 manufacturing (≤ 50, > 50 kg)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Child bearing status (premenarche, able to bear children, sterile – of child bearing age)
- Disease status at study entry (refractory, relapsed)
- Time since initial diagnosis of ALL to first relapse/progression (< 18 months, ≥ 18 to ≤ 36 months, > 36 months)

In addition, for the legal requirements of clinicaltrials.gov and EudraCT, the following age categories will also be presented:

- Infants and toddlers, 28 days to <2 years
- Children, ≥2 to <12 years
- Adolescents, ≥12 to <18 years
- Adults, ≥18 to < 65 years

2.3.2.1 ALL characteristics

The CD19 status, MRD status, local morphologic blast count, central nervous system (CNS) classification and other extramedullary disease status prior to enrollment will be summarized overall and by the subgroup age at screening (defined in Section 2.2.1).

The number and percentage of patients with CNS involvement by ALL at any time prior to enrollment will be summarized.

Other CNS disease history (usually non-leukemic, refer to [CSR Appendix 16.1.1-Protocol-Section 5.8]) and CNS related prior radiotherapy (e.g. to the brain or cranial spinal axis) will also be summarized.

2.3.2.2 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms at the time of informed consent will be summarized.

Ongoing and historical medical conditions will be flagged separately in the listing for the ENS.

The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical histories are coded using the most recent (i.e. latest version as per CDBL) Medical Dictionary for Regulatory Activities (MedDRA). The primary SOCs will be presented in alphabetical order and the PTs will be presented by decreasing proportion.

2.3.2.3 Prior anti-neoplastic therapy

Prior anti-neoplastic medications will be identified by anatomical therapeutic chemical (ATC) class and PT according to the most recent version (i.e. latest version as per CDBL) of the World Health Organization (WHO) Drug Reference List dictionary.

The number and percentage of patients with prior anti-neoplastic medications/therapies (including medications for hematological disease, surgery, radiotherapy and HSCT) will be summarized. Number of previous complete remissions, number of previous lines of therapies, setting of last medication (induction, consolidation, maintenance, salvage, conditioning for HSCT), best response of last medication and locations of last radiotherapy will also be summarized. In addition the following will also be summarized:

- Time since last surgery to CTL019 infusion (< 1 month, 1 to < 6 months, 6 to < 12 months, ≥ 12 months)
  - Defined as: (date of CTL019 infusion – date of last surgery prior to CTL019 infusion + 1) / 30.4375

In addition, the number and percentage of patients with prior antineoplastic blinatumomab and inotuzumab will be summarized separately. The cumulative dose of blinatumomab prior to enrollment, the number of cycles of blinatumomab prior to enrollment, the cumulative dose of inotuzumab prior to enrollment and the number of cycles of inotuzumab prior to enrollment will also be summarized. Inotuzumab may have been used as a bridging therapy prior to CTL019 infusion; therefore, the number and percentage of patients with inotuzumab as bridging therapy prior to CTL019 infusion will be presented along with the cumulative dose of inotuzumab used as bridging therapy prior to CTL019 infusion and the number of cycles of inotuzumab used as bridging therapy prior to CTL019 infusion. In addition, the following will be presented:

- Time since last blinatumomab infusion prior to enrollment to CTL019 infusion (days)
  - Defined as: (date of CTL019 infusion – date of last day blinatumomab cycle prior to enrollment + 1)
- Time since last inotuzumab prior to enrollment to CTL019 infusion (days)
  - Defined as: (date of CTL019 infusion – date of last day inotuzumab cycle prior to enrollment + 1)
- Time since last inotuzumab as bridging therapy to CTL019 infusion (days)
  - Defined as: (date of CTL019 infusion – date of last day inotuzumab cycle as bridging therapy + 1)

Prior anti-neoplastic medications for hematological disease will be summarized by ATC class and PT. The ATC class will be presented in alphabetical order and PTs by decreasing proportion.

All prior anti-neoplastic medications, radiotherapy and HSCT will be listed for the ENS. The number of previous complete remissions and number of previous lines of therapies will also be listed.

2.3.2.4 Cytogenetic abnormalities

The number and percentage of patients with cytogenetic abnormalities (yes/no) and those with complex karyotypes (≥ 5 unrelated abnormalities) at study entry will be summarized. The type of cytogenetic abnormalities will also be presented.

All cytogenetic abnormalities will be listed for the ENS.

2.3.3 Protocol deviations

The number and percentage of patients with any protocol deviation will be tabulated by deviation category. Major protocol deviations leading to exclusion from the analysis sets will be summarized. Patients with multiple protocol deviations will only be counted once at each level of summarization. All protocol deviations will be listed for the ENS.

In addition pandemic related protocol deviations will be summarized by category and relationship. All COVID-19 related protocol deviations will also be listed for the ENS.

2.3.4 Others

All other data collected at baseline will be listed.

2.4 Treatments (program treatment, concomitant therapies, compliance)

Summaries will be presented for the SAF, unless otherwise specified.

2.4.1 Study treatment / compliance

The total cells infused (in cells), total CTL019 transduced viable T-cell count (in cells and 10^8 cells/kg) and actual percentage volume (%) infused will be listed and summarized overall and by the subgroup age at screening (defined in Section 2.2.1) using descriptive statistics. Note: The weight provided to the manufacturing facility for CTL019 product manufacturing will be used for calculating the weight adjusted doses (10^6 cells/kg).

Patients will be categorized as below, within or above the prescribed dose range by body weight stratum (i.e. ≤ 50 kg and > 50 kg).

Patients with dose interruptions, as recorded in the dosage administration record eCRF, will be listed.

Because CTL019 is administered via one time infusion, no specific compliance will be summarized other than the CTL019 dose administration.

In addition, the total duration of study follow-up for the SAF will be summarized numerically as well as by categories: < 6 months, 6 months to < 12 months, ≥ 12 months.

2.4.2 Prior, concomitant and post therapies

Medications will be identified by ATC class and PT according to the most recent version (i.e. latest version as per CDBL) of the WHO Drug Reference List dictionary.

Prior and concomitant medications and non-drug therapies will be captured with start and stop dates in the eCRF.

- Prior medications: Medications that have an end date prior to the start of CTL019 infusion on Study day 1.
- Concomitant medications:
  - Medications that started on or after start of CTL019 infusion on Study day 1, or
  - Medications that started prior to the start of CTL019 infusion and continued during the post-infusion follow-up period.

Prior and concomitant medications and significant non-drug therapies prior to and after the start of infusion will be listed by patient and summarized by ATC class and PT. The ATC class will be presented in alphabetical order and the PTs will be presented by decreasing proportion.

Antineoplastic therapies, including the lymphodepleting chemotherapies, received after enrollment but prior to infusion will be listed. Patients will also be summarized by the types of lymphodepleting chemotherapies received (i.e. fludarabine-based lymphodepleting therapy, non-fludarabine based lymphodepleting therapy and no lymhodepleting therapy).

Transfusion data collected during the study will be listed for the ENS.

In addition, the use/non-use of anti-cytokine medications for the management of CRS will be summarized. These anti-cytokine medications are given for severe CRS due to CTL019 cells.

The number and percentage of patients with post CTL019 infusion HSCT will be summarized along with the graft, transplant and allogeneic donor type. Disease type and MRD status prior to receiving HSCT as well as best hematologic response status and MRD status post HSCT will also be summarized. In addition the following will also be summarized:

- Time since CTL019 infusion to post HSCT
  - Defined as: (date of post CTL019 infusion HSCT - date of CTL019 infusion + 1) / 30.4375

2.5 Analysis of the primary objective

The primary objective of the program is to evaluate descriptively the safety of CTL019 therapy. The assessment of safety will include all treatment-emergent AEs (TEAEs) including serious adverse events (SAEs) and laboratory abnormalities occurring from screening through to the end of study (Month 12)/Early Withdrawal.

The primary analysis will be based on the SAF only.

2.5.1 Primary endpoint

The primary variable is overall TEAEs (including SAEs and laboratory abnormalities observed after CTL019 infusion). Treatment-emergent AEs are defined as AEs that started or worsened after the infusion of CTL019.

2.5.2 Statistical hypothesis, model, and method of analysis

No statistical hypothesis testing is planned for the primary variable.

2.5.2.1 Adverse events

Reporting of AEs (except for CRS) will be based on MedDRA (latest version as per database lock) and Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher.

The grading of CRS will be based on protocol specific grading scales ([CSR Appendix 16.1.1-Protocol-Section 6.2.1.1, Table 6-1]).

The following table summarizes the mutually exclusive safety reporting periods for AEs as well which patients should be included for each period.

Table 2-2 Safety reporting periods

Period	Definition	Patients to be included
Pre-treatment period	From informed consent date to the day before first lymphodepleting chemotherapy dose or the pre-infusion visit (if no lymphodepleting chemotherapy is given)	Screened Set
Lymphodepleting period (Note: This period only applies to patients who received lymphodepleting chemotherapy)	From the first day of lymphodepleting chemotherapy • to the day before infusion of CTL019, for patients who received infusion or • to the earlier of the date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy, for patients who didn't receive infusion of CTL019	All patients who received lymphodepleting chemotherapy
Post CTL019 infusion period	From first CTL019 infusion date until end of study	SAF

Only TEAEs will be summarized, i.e. those AEs in the post CTL019 infusion period (see Table 2-2 for definition). However, all safety data will be listed and with the period flagged for the starting date of the AE.

TEAEs will be summarized by presenting the crude incidence of subjects having any TEAE and having a TEAE by primary SOC and by PT. Patients who experienced multiple AEs for a PT will be counted once for that PT, similarly for patients with multiple AEs per primary SOC. A patient with multiple CTCAE grades for an AE will be summarized under the maximum CTCAE grade recorded for the event. The frequency of CTCAE grade 3 and 4 AEs will be summarized separately.

Post CTL019 infusion period

The incidence of TEAEs will be summarized for the SAF as follows:

- Adverse events, regardless of CTL019 relationship, by primary SOC, PT and maximum CTCAE grade.
- Adverse events, regardless of CTL019 relationship, by primary SOC, PT, maximum CTCAE grade and age at screening (age at screening subgroup is defined in Section 2.2.1).
- Adverse events, suspected to be CTL019 related, by primary SOC, PT and maximum CTCAE grade.
- Serious AEs, regardless of CTL019 relationship, by primary SOC, PT and maximum CTCAE grade.
- Serious AEs, suspected to be CTL019 related, by primary SOC, PT and maximum CTCAE grade.
- Adverse events requiring medication or therapies, regardless of CTL019 relationship, by primary SOC, PT and maximum CTCAE grade.
  Note: Medication or therapies refers to additional therapy.

Treatment emergent AEs will be summarized by timing of onset:

- Within 8 weeks post CTL019 infusion.
- Any time post CTL019 infusion (Note: Any time post CTL019 infusion will include the time period within 8 weeks post CTL019 infusion).

In addition, for the legal requirements of clinicaltrials.gov and EudraCT, 2 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 study treatment will be provided by primary SOC and PT.

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 study treatment/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.

2.5.2.2 Deaths

The number and percentage of post-infusion deaths will be summarized by primary SOC and PT. Deaths will also be listed by reason.

2.5.2.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE, the biostatistics and programming team will grade laboratory data accordingly; a Grade 0 will be assigned for all non-missing values not graded as 1 or higher, and Grade 5 will not be used.

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.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Shift tables using CTCAE grades to compare baseline to the worst post-infusion value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

In addition, the number and percentage of patients with Grade 3 or 4 hematopoietic cytopenias 28 days post CTL019 infusion will be summarized. Among patients with Grade 3 or 4 hematopoietic cytopenias 28 days post CTL019 infusion, the timing of resolution to Grade 2 or below will be summarized via Kaplan-Meier (KM) method. Grading of cytopenias will be derived using laboratory results in absolute lymphocytes (hypo), absolute neutrophils (hypo), hemoglobin (hypo), platelet count (hypo) or WBC (hypo) according to CTCAE 4.03. If a patient did not achieve resolution at the last laboratory assessment, the timing of resolution will be censored at the last assessment. The median time to resolution and KM estimates of % unresolved cases at different time points (Month 2, Month 3, etc.) will be summarized.

2.5.3 Handling of missing values/censoring/discontinuations

All available data will be used in these evaluations of safety. No imputation will be done for missing AE data with exception of AE data imputation outlined in Section 5.6.1.

2.5.4 Supportive analyses

No supportive analyses are planned for the primary objective.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of the secondary efficacy objectives

The efficacy endpoints will be analyzed based on the FAS, unless otherwise specified.

2.7.1 Secondary endpoints

The analysis of the secondary endpoints is described below.

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 Proportion of patients who achieve complete remission during 6 months after CTL019 infusion

The objective is based on the ORR (CR or CRi) as determined by the investigator (based on the definitions outlined in Table 2-3) during the 6 months after CTL019 infusion. The ORR is defined as the proportion of patients with a best overall disease response of CR or CRi, where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until Month 6. Best overall disease response will be assigned according to the following order:

- CR
- CRi
- No response (NR)
- Unknown

Table 2-3 Definition of CR, CRi and relapse at a given evaluation time

Response category	Definition
CR	All the following criteria are met: **Bone marrow** < 5% blasts **Peripheral blood** Neutrophils > 1.0×10^9/L, and Platelets > 100×10^9/L, and Circulating blasts < 1% **Extramedullary disease** No evidence of extramedullary disease (by physical examination and CNS symptom assessment) **Transfusion independency** No platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
CRi	All criteria for CR as defined above are met, except that the following exist: • Neutrophils ≤ 1.0×10^9/L, and/or • Platelets ≤ 100×10^9/L, and/or • Platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Relapsed disease	Only in patients who obtained a CR or CRi: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi

The proportion of patients who achieve complete remission, which includes CR or CRi during the 6 months after CTL019 infusion, will be summarized along with 2-sided exact (Clopper-Pearson) 95% CIs. The aforementioned analysis will also be repeated for the PPS.

In addition, the main analysis will be performed on subgroups outlined in Section 2.2.1.

2.7.2.2 Percentage of patients who achieve CR or CRi at Month 6 without HSCT between CTL019 infusion and Month 6 response assessment

The number and percentage of patients who achieve complete remission (CR or CRi) at Month 6 without HSCT (post CTL019 infusion) between CTL019 infusion and Month 6 response assessment will be summarized along with 2-sided exact (Clopper-Pearson) 95% CIs.

The patient will be considered to be in complete remission (CR or CRi) at Month 6 if there is at least one CR or CRi assessment after Day 167 (i.e. >30.4375 × 5.5) without any relapse prior to this CR or CRi assessment. If such a patient does not have HSCT prior to Month 6, this patient is considered as having achieved complete remission (CR or CRi) at Month 6 without HSCT between CTL019 infusion and Month 6 response assessment.

The time of proceeding to HSCT is defined as the time of commencing the conditioning regimen as required for HSCT. This definition applies to all analyses involving HSCT.

2.7.2.3 Percentage of patients who achieve CR or CRi and then proceed to HSCT while in remission before Month 6 response assessment

The number and percentage of patients who achieve complete remission (CR or CRi) and then proceed to HSCT while in remission by the time of Month 6 will be summarized along with 2-sided exact (Clopper-Pearson) 95% CIs. Note: The "Month 6" evaluation is as defined in Section 2.7.2.2.

For patients who discontinue and undergo HSCT before the scheduled Month 6 evaluation, they will be considered to have met this secondary endpoint if the patients are still in morphologic remission, i.e. the DOR is not lost or censored.

2.7.2.4 Duration of remission

Duration of remission (DOR) is defined as the duration from the date when the response criteria of CR or CRi is first met to the date of relapse or death due to underlying cancer, whichever occurs first.

Definition of relapse

Relapse is defined as:

- Reappearance of blasts in the blood (≥ 1%), or
- Reappearance of blasts in bone marrow (≥ 5%), or
- (Re-)appearance of any extramedullary disease after CR or CRi.

That is, first relapse either on the following:

- Bone marrow assessment
- Peripheral blood assessment
- Extramedullary disease assessment, including
  - CNS disease
  - Other extramedullary sites
  - MRD assessment of bone marrow

In the main analysis of DOR, in case a patient does not have relapse or death due to ALL prior to analysis data cut-off, the DOR will be censored at the date of the last adequate assessment on or prior to the earliest censoring event (except for HSCT). The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available
- New anticancer therapy other than reinfusion with one or more additional CTL019 dose/s (with or without lymphodepleting chemotherapy) (also see below for handling HSCT)
- Event after at least 2 missing scheduled disease assessments

As HSCT is an important treatment option in responding patients, it is appropriate to consider the date of HSCT as the censoring date, instead of censoring at the last tumor assessment date.

A sensitivity analysis will be performed in which the date of relapse or death (if due to the underlying cancer) after HSCT will be used for the calculation of DOR, if there is at least 1 patient with HSCT after CTL019 infusion while in remission. If a patient received HSCT after a CR or CRi, relapse after HSCT will be recorded in the corresponding follow-up eCRF, although data on individual disease response components (e.g. bone marrow) will not be collected. Censoring due to HSCT will overestimate the rate of relapse and therefore may be considered inappropriate for the main analysis when a substantial number of patients choose to receive HSCT (CHMP 2010). Therefore the above described sensitivity analysis will be performed if there is at least 1 patient with HSCT after CTL019 infusion while in remission.

Duration of remission will be assessed only in patients with the best overall response of CR or CRi. The estimated percentage of relapsed patients (at 6 months, 12 months, etc.) will be presented with 95% CIs using the KM method.

In addition, the site of involvement of subsequent relapse after remission will be summarized.

The main analysis will also be performed on the subgroups outlined in Section 2.2.1.

The duration of follow-up for DOR (see Section 5.3) and the reasons for censoring will also be presented for the FAS.

2.7.2.5 Relapse free survival

Relapse free survival is measured by the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to any cause during CR or CRi.

In case a patient does not have relapse or death due to any cause prior to the analysis data cutoff, RFS will be censored at the date of the last adequate assessment on or prior to the earliest censoring event (except for HSCT). The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy other than reinfusion with one or more additional CTL019 dose/s (with or without lymphodepleting chemotherapy) (also see below for handling HSCT)
- Event after at least 2 missing scheduled disease assessments

In the main analysis of RFS, patients who proceed to HSCT after CTL019 infusion will be censored at the time of HSCT. In addition, a sensitivity analysis of RFS will be performed without censoring HSCT, if there is at least 1 patient with HSCT after CTL019 infusion while in remission.

Relapse free survival will be assessed only in patients with the best overall response of CR or CRi. The distribution function of RFS will be estimated using the KM method. The median RFS along with 95% CIs will be presented as appropriate.

The duration of follow-up for RFS (see Section 5.3) and the reasons for censoring will also be presented for the FAS.

2.7.2.6 Event free survival

Event free survival is the time from date of first CTL019 infusion to the earliest of the following:

- Death from any cause
- Relapse
- Treatment failure: defined as NR in the study and discontinuation from the study due to any of the following reasons:
  - Death
  - Adverse event (including abnormal laboratory values or abnormal test procedure results)
  - Lack of efficacy or progressive disease
  - New anticancer therapy

In case of treatment failure, the event date will be set to Study day 1 (CHMP 2010). In addition, a sensitivity analysis of EFS will be performed by considering time of discontinuation from the study as the event time for treatment failure, instead of setting to Study day 1.

In case a patient does not have relapse, death due to any cause or treatment failure (e.g. discontinuation as a result of withdrawal of consent, loss to follow-up, protocol violation or administrative problems) prior to analysis data cut-off, EFS is censored at the last adequate response assessment date on or prior to the earliest censoring event (except for HSCT). The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy other than reinfusion with one or more additional CTL019 dose/s (with or without lymphodepleting chemotherapy) (also see below for handling HSCT)
- Adequate assessment no longer available
- Event after at least 2 missing scheduled disease assessments

In the main analysis of EFS, patients who proceed to HSCT after CTL019 infusion will be censored at the time of HSCT. In addition, a sensitivity analysis of EFS will be performed without censoring HSCT, if there is at least 1 patient with HSCT after CTL019 infusion while in remission.

The distribution function of EFS will be estimated using the KM method. The median EFS along with 95% CIs will be presented if appropriate.

In addition, the main analysis will be performed on the subgroups outlined in Section 2.2.1.

The duration of follow-up for EFS (see Section 5.3) and the reasons for censoring will also be presented for the FAS.

2.7.2.7 Overall survival

Overall survival is the time from date of first CTL019 infusion to date of death due to any reason.

In case a patient is alive at the date of last contact on or before the data analysis cut-off, OS is censored at the date of last contact. No censoring will be done in case of HSCT for the main analysis. A sensitivity analysis of OS will be performed censoring HSCT, if there is at least 1 patient with HSCT after CTL019 infusion while in remission.

The distribution function of OS will be estimated using the KM method. The median OS along with 95% CIs will be presented if appropriate.

The duration of follow-up for OS (see Section 5.3) and the reasons for censoring will also be presented for the FAS.

2.7.2.8 Response at Day 28 ± 4 days

The proportion of patients attaining CR or CRi at Day 28 ± 4 days post CTL019 infusion will be summarized along with 2-sided exact (Clopper Pearson) 95% CIs.

2.7.2.9 Impact of baseline tumor burden on response

The disease response at Day 28 ± 4 days will be summarized by baseline tumor burden (i.e. by the subgroup baseline bone marrow tumor burden).

2.7.2.10 Quality of response using MRD assessments

The quality of response using MRD assessments (i.e. proportion of patients with MRD negative disease response) before treatment, and at Day 28 ± 4 days after treatment by flow cytometry and before HSCT by local assessment (flow or qPCR) will be summarized descriptively. The proportion of patients with MRD negative will be summarized along with 2-sided exact (Clopper Pearson) 95% CI.

Qualitative results (positive/negative) will be summarized if available.

2.7.2.11 Immunogenicity

Humoral immunogenicity

The humoral immunogenicity assessment will include evaluation of pre-existing (pre-treatment) and post-treatment anti-CTL019 antibodies to examine the incidence of immunogenicity with treatment, together with antibody titers, as a secondary endpoint. Data may be further fractionated to determine the proportion of patients who make transient versus sustained antibody responses. The titer fold-change from baseline will be determined for each patient.

The proportion of humoral immunogenicity positive and negative patients will be summarized by time point overall and by Day 28 ± 4 days disease response. A strip plot of anti-CTL019 antibodies by time point will also be provided.

[redacted]

[redacted]

2.8 Safety analyses

The primary objective of this study is overall TEAEs and corresponding analysis methodologies as specified in Section 2.5.

In this section, the description of other safety analyses is specified. For all safety analyses, the SAF will be used.

2.8.1 Adverse events

See Section 2.5.2.1 for details.

2.8.2 Deaths

See Section 2.5.2.2 for details.

2.8.3 Laboratory assessments

All laboratory abnormalities occurring post-infusion comprises of the category of TEAEs and are reported as a part of the primary analysis as specified in Section 2.5.2.3. Any laboratory abnormality occurring pre-infusion will be flagged in the respective listing.

2.8.4 Cytokine release syndrome and anti-cytokine therapies

Detailed information regarding the CRS will be summarized overall and by Day 28 ± 4 days overall disease response. Information summarized will include: maximum CRS grade, time to onset of CRS; duration of CRS; time to Grade 3/4 CRS, concurrent infections, timing and duration of intensive care unit (ICU) stay, selected complications, and use of anti-cytokine therapies, etc.

2.8.5 Apheresis product processing and CTL019 product characteristics

The total cell count and CD3+CD45+ (%) will be listed and summarized for apheresis product processing.

The following product characteristics for the manufactured product will be listed and summarized:

- Cell viability on sentinel vial (%)
- CD3+CD45+ (%)
- Transduction efficiency (%)
- Vector Deoxyribonucleic Acid (DNA) sequence: CTL019 PCR (copies/cell)
- Vesicular Stomatitis Virus, Glycoprotein (VSV-g) DNA: Replication Competent Lentivirus (RCL), value (copies/ug DNA)

In addition the number (and reason) of products not meeting safety or other criteria will be presented.

Data related to the cryopreservation of cell doses will be listed.

2.8.6 Other safety data

Other safety data will be listed by subject.

2.9 Pharmacokinetic endpoints

2.9.1 Cellular kinetics

CTL019 concentrations in the peripheral blood, as measured by qPCR, will be graphed, and summarized by time point for the CKAS.

The cellular kinetic parameters listed in Table 2-4 along with other relevant cellular kinetic parameters will be estimated from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix® (Pharsight, Mountain View, CA). The non-quantifiable concentrations will be imputed to zero for concentration summaries, and will not be included for estimation of cellular kinetic parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and parameter derivations.

Table 2-4 Non-compartmental cellular kinetic parameters

Parameter	Definition
$AUC_{0 - D28 \text{ and } M3}$	The AUC from time zero to Day 28 and Month 3 or other disease assessment days, in peripheral blood (copies/µg x days)
C_{max}	The maximum (peak) observed in peripheral blood drug concentration after single dose administration (copies/µg)
C_{last}	The last observed quantifiable concentration in peripheral blood (copies/µg)
T_{max}	The time to reach maximum (peak) peripheral blood drug concentration after single dose administration (days)
$T_{1/2}$	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
T_{last}	The time of last observed quantifiable concentration in peripheral blood (days)

Descriptive statistics of the CK parameters will be summarized by mean, standard deviation, coefficient of variation, geometric mean, CV% geometric mean, median, min and max, overall and by Day 28 ± 4 days disease response. When a geometric mean will be presented, it will be stated as such. A range of values will be presented for selected variables. Since T_{max} and T_{last} are generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

The relationship of C_{max} and $AUC_{0\text{-}28d}$ of CTL019 in the blood with CRS grade will be assessed.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

2.12.1 B-cell and T-cell levels

The levels (%) of CD19+ total B-cells amongst viable white blood cells (WBCs) (peripheral blood) prior to and following CTL019 infusion will be described by time point, overall and by Day 28 ± 4 days disease response. The levels (%) of T-cells amongst mono-nuclear cells (lymphocytes and monocytes with the exclusion of granulocytes) in peripheral blood will also be described by time point.

It is anticipated that all patients who achieve complete remission will exhibit B-cell aplasia. Timing of B-cell recovery will also be summarized. B-cell recovery is defined as the time from onset of remission date to the earliest time when the percentage of CD19+ total B-cell among viable WBC in blood is at least 1%, or the percentage of CD19+ total B-cell among lymphocyte in blood is at least 3%. If no B-cell recovery is observed, the time to B-cell recovery will be censored at the last B-cell result. Note: If CD19+ ALL tumor cells are also present in the blood (recurrence), total B-cells are affected by the malignant B-cells and hence should be interpreted with caution.

For abnormal B-cell results, associated safety events such as infections and use of associated therapies (i.e. antibiotics, immunoglobulin replacement) will be investigated using patient listings.

2.13 Other exploratory analyses

Not applicable.

2.14 Interim analysis

No interim analysis is planned for the program. The safety data will be reviewed periodically.

3 Sample size calculation

There is no formal sample size calculation performed for this study. This study aims to provide pediatric/young adult patients with relapsed or refractory B-cell ALL the opportunity to be treated with CTL019 after the closure of the Novartis single-arm phase II clinical trial CTL019B2202. The primary objective is to evaluate descriptively the safety of CTL019 and no testing of hypothesis will be performed.

The sample size is projected based on the availability of eligible patients who have provided an acceptable leukapheresis product of non-mobilized cells to the manufacturing site and by the capacity of manufacturing CTL019 product in the Novartis facility at an average of 2 slots per month. It is anticipated that the recruitment duration will be ~ 2 years. Based on this assumption, and assuming that the average number of slots may increase as the program progresses, it is anticipated that approximately 80 patients will be enrolled in this study.

4 Change to protocol specified analyses

It was clarified that reference to:

- New anticancer therapy refers to new anticancer therapy other than reinfusion with one or more additional CTL019 dose/s (with or without lymphodepleting chemotherapy).
- SCT refers to HSCT.

In addition the team confirmed that all analyses will be performed after all patients have received CTL019 infusion and completed 12 months post-infusion of CTL019, or prematurely discontinued before the end of the follow-up period. A final CSR will be produced once all patients complete the study. An interim publication analysis was performed on 3-month post-infusion data.

MRD quantitative data are not collected in this study; reference to these data as part of the secondary endpoints has been updated to remove this.

The team confirmed that an analysis of selected clinical outcomes by CTL019 is not of clinical interest; hence it was removed.

CR rate was replaced with ORR to align with other CTL019 studies.

Any reference to pharmacokinetics was removed from the CKAS.

The minimum target dose reference for the PPS has been updated to align with the protocol.

The safety subgroup analyses are no longer of clinical interest to the team; they have therefore been removed.

All TEAE summary tables will be produced for the SAF not FAS.

Any data analysis based on combining data collected in this protocol together with the 15-year LTFU protocol is not part of this SAP or final CSR.

5 Appendix

5.1 Response rate analyses

For the analyses of response rate (e.g, CR), the rates will be summarized along with a 2-sided 95% exact Clopper-Pearson CI. Sample code is provided below.

```
PROC FREQ data=dataset;
TABLES outcome/binomial(CL=exact);
RUN;

/* outcome is the variable to indicate response or not, note that if the outcome
is dichotomous variable, then the proportion of outcome=0 will be calculated.*/
```

5.2 Time-to-event analyses

For time-to-event analyses, the survival or failure function will be estimated using the KM (product-limit) method as implemented in PROC LIFETEST (see examples below). Median survival will be obtained along with 95% CIs calculated from PROC LIFETEST output using the loglog option available within PROC LIFETEST, Kaplan-Meier estimates with 95% CIs at specific time points will be summarized.

```
PROC LIFETEST data=dataset METHOD=KM conftype=loglog;
TIME survtime*censor(1);
RUN;

/* survtime represents variable containing event/censor times;
censor represents censoring variable (1=censored, 0=event); */
```

The time points can be expressed in weeks or in months depending on the time-to-event variable (e.g. OS might require a different scale than duration of response). If 'months' is used it should be noted that 1 month is defined as (365.25/12) =30.4375 days, which is not equal to 4 weeks.

5.3 Duration of follow-up

For time to event the follow up time (in months) will be calculated as:

- DOR and RFS: Follow-up time = (Date of event or censoring - Date of first occurrence of CR or CRi + 1)/30.4375.
- EFS and OS: Follow-up time = (Date of event or censoring - Date of first CTL019 infusion + 1)/30.4375.

The study follow up duration (in months) will be calculated as:

- (Analysis cut-off date – Date of first CTL019 infusion + 1)/30.4375.

5.4 Baseline bone marrow tumor burden

Baseline bone marrow tumor burden will be derived using the following:

- Select the baseline morphologic result; this refers to the latest blast cells assessment prior to enrollment.
  - Bone marrow aspirate assessment: Select the latest result prior to enrollment.
  - Bone marrow biopsy assessment: Select the latest result prior to enrollment.

  Choose the blast cells (%) value from each of the two assessments mentioned above; if it is missing but at the same visit and evaluation the blast cells absolute value is available, select the absolute value and convert it to % using the following definition:

  % value = (absolute value/number of cells counted)*100
- If the baseline dates for the bone marrow aspirate and bone marrow biopsy assessments are not the same, select the blast cells (%) value closest to the enrollment date. Otherwise select the maximum blast cells (%) value from the bone marrow apsirate or bone marrow biopsy assessments.

- Once the baseline value is selected, it will be categorized into:
  - Low (baseline morphologic result < 50%)
  - High (baseline morphologic result ≥ 50%)

5.5 Time windows

In order to summarize the disease assessment and CK data over time, assessments will be time-slotted using the following time windows. These windows will be based on the study evaluation schedule and should comprise a set of days "around" the nominal visits. As a general rule, the following steps are followed to determine the cut-offs for post-baseline time windows:

- Transform all scheduled assessment time points into study days, assuming 1 month = 30.4375 days. Middle points of scheduled assessments are determined.
- The time window associated with the previous assessment ends prior to the middle point; the time window associated with the latter assessment begins after the middle point. In case the middle point is an exact study day, it will belong to the previous assessment.
- The time window of the first post-baseline assessment starts with Day 2, unless otherwise indicated.

If more than one assessment is done within the Baseline time window, the last assessment in the baseline time window will be used. For all other time windows, the assessment closest to the planned assessment date will be used; if 2 or more assessments are equidistant from the planned date, then the mean value will be used.

[CSR Appendix 16.1.1-Protocol-Section 7.2.3] shows the defined time points for sample collections and related information in addition to the tables below that will be considered by statistical programming.

Table 5-1 Time windows for disease assessments

Time Window	Planned visit timing (study day)	Time Window Definition (Study days)
Peripheral blood for serum cytokine analyses		
W-16 to D-1 Enrollment/Pre-Chemotherapy*	Before Study Day -1	< first day of Lymphodepleting (LD) chemotherapy
D -1 Pre-infusion**	-1	Day of LD chemo to day 1 pre infusion
D7±1d	7	Day 1 post infusion to 10
D14±3d	14	11 to 17
D21±3d	21	18 to 24
D28±4d	28	25 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 273
M12±14d	365	≥274
CTL019 Immunophenotyping; B-cell; T-cell (peripheral blood)		
W-16 to D-1 Enrollment/Pre-Chemotherapy *	Before Study Day -1	< first day of Lymphodepleting (LD) chemotherapy
D -1 Pre-infusion**	-1	Day of LD chemo to day 1 pre infusion
D7±1d	7	Day 1 post infusion to 10
D14±3d	14	11 to 17

Time Window	Planned visit timing (study day)	Time Window Definition (Study days)
D21±3d	21	18 to 24
D28±4d	28	25 to 59
M3±14d (Primary follow-up only)	91	60 to 136
M6±14d (Primary follow-up only)	183	137 to 228
M9±14d (Primary follow-up only)	274	229 to 319
M12±14d (Primary follow-up only)	365	320 to 574
Tumor clonal analysis by deep sequencing (peripheral blood)		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	< first day of Lymphodepleting (LD) chemotherapy
D28±4d	28	21 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 273
M12±14d	365	≥274
Tumor clonal analysis by deep sequencing (bone marrow aspirate); CTL019 Immunophenotyping; B cell; T cell (bone marrow aspirate); MRD assessment in bone marrow (flow cytometry; qPCR)		
W-16 to W-12 Screening*	Before Study Week -12	< first day of Lymphodepleting (LD) chemotherapy
D28±4d	28	21 to 59
M3±14d (recommended but not required)	91	60 to 136
M6±14d (recommended but not required)	183	≥137

Study Day 1 = start date of CTL019
* for patients who didn't receive LD chemotherapy, this window is ≤-2
**for patients who didn't receive LD chemotherapy, this window is -1 to 1 pre-infusion

Table 5-2 shows the defined time windows for CTL019 CK samples including the samples collected during CRS after administration of tocilizumab and siltuximab.

Table 5-2 Time windows for CTL019 CK

Time Window	Planned visit timing (Study day)	Time Window Definition (Study day)
CTL019 cellular kinetics by qPCR (peripheral blood)		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤ day 1 pre-infusion
D1 10 min ± 5 min post-infusion	1	Day 1 post-infusion to 2
D4±1d	4	3 to 5
D7±1d	7	6 to 9
D11±1d	11	10 to 12
D14±3d	14	13 to 20
D28±4d	28	21 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 228
M9±14d	274	229 to 319
M12±14d	365	320 to 456

Table 5-3 shows the defined time windows for CTL019 CK sample.

Table 5-3 Time windows for immunogenicity assessments

Time Window	Planned visit timing (Study day)	Time Window Definition (Study day)
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤-1
D1±1d	1	Day 1 post-infusion to 2
D14±3d	14	3 to 21
D28±4d	28	22 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 273
M12±14d	365	274 to 574
Study Day 1 = start date of CTL019		

Table 5-2 shows the defined time windows for laboratory assessment.

Table 5-4 Time windows for laboratory assessments

Time Window	Planned visit timing (Study day)	Time Window Definition (Study day)
Hematology		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤ day 1 pre-infusion
D1	1	Day 1 post-infusion to 2
D4±1d	4	3 to 5
D7±1d	7	6 to 10
D14±3d	14	11 to 20
D28±4d	28	21 to 46
M2±14d	61	47 to 76
M3±14d	91	77 to 106
M4±14d	121	107 to 136
M5±14d	151	137 to 166
M6±14d	183	167 to 228
M9±14d	274	229 to 319
M12±14d	365	320 to 456
Chemistry		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤ day 1 pre-infusion
D1	1	Day 1 post-infusion to 2
D4±1d	4	3 to 5
D7±1d	7	6 to 10
D14±3d	14	11 to 20
D28±4d	28	21 to 46
M2±14d	61	47 to 76
M3±14d	91	77 to 136
M6±14d	183	137 to 273
M12±14d	365	274 to 574
Coagulation		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤ day 1 pre-infusion
D1	1	Day 1 post-infusion to 2

Time Window	Planned visit timing (Study day)	Time Window Definition (Study day)
Hematology		
D7±1d	7	3 to 10
D14±3d	14	11 to 20
D28±4d	28	21 to 46
M2±14d	61	47 to 76
M3±14d	91	77 to 106
M4±14d	121	107 to 136
M5±14d	151	137 to 166
M6±14d	183	167 to 228
M9±14d	274	229 to 319
M12±14d	365	320 to 456
Serum Immunoglobin		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤ day 1 pre-infusion
D28±4d	28	1 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 228
M9±14d	274	229 to 319
M12±14d	365	320 to 456
Urinalysis, Microscopic analysis		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤ day 1 pre-infusion
Study Day 1 = start date of CTL019		

5.6 Handling of missing or partial dates

Missing or partial date imputation will be conducted according to the logic described in this section. The imputed dates will be used for the calculation of duration of events. However, in the listings only the original reported dates will be listed.

5.6.1 Adverse event date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. The missing date(s) for AE(s) will be handled according to the rules specified below. A partial date is simply an incomplete date e.g. DDOCT2001: the days are missing from this DDMMMYYYY date.

Partial AE start dates, if left partial, would ultimately mean the following:

It would not be possible to place the AE in time. Therefore the treatment/dosage at the time of the event would be unknown. Therefore the event could not be reported/summarized appropriately – if at all. Therefore it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course partial and/or missing dates should also be caught as edit checks and passed back to the investigator for resolution.

The AE start date will be imputed as follows:

The following Table 5-5 explains the abbreviations used.

Table 5-5 Adverse event/treatment date abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 5-6 describes the possible combinations and their associated imputations. In the table body the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-6 Adverse event partial date imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The following Table 5-7 is the legend to the above table.

Table 5-7 Adverse event/treatment date relationship and imputation legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 5-8 gives a few examples.

Table 5-8 Adverse event imputation example scenarios

Partial AE start date	Treatment start date	Relationship	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

Note, it may happen that the imputed AE start is after AE end date, in that case, imputed AE start=AE end date.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**

Partial AE end date will be imputed as follows:

- Imputed date = min (date of death if applicable, last day of the month), if day is missing;
- Imputed date = min (date of death if applicable, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Missing AE end date or AE end date after the analysis data cut-off will be imputed as follows:

All events with start date before or on the analysis cut-off date, and with end date missing or after the analysis cut-off date will have the end date imputed as the minimum of the analysis cut-off date, end of study evaluation (i.e. completion of the last phase of the study) or date of death (if applicable). For these events, the imputed end date will not appear in the listings, instead, they will be reported as “continuing”.

5.6.2 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as described for the AE date. Partial concomitant medication end dates will not be imputed.

5.6.3 Incomplete date for anti-neoplastic therapies

Prior therapies

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be 'start date of study treatment -1'.

End date:

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Post therapies

Start date:

Imputed date = max (last date of study treatment + 1, first day of the month), if day is missing;

Imputed date = max (last date of study treatment + 1, 01JAN), if day and month are missing.

End date: No imputation.

5.6.4 Incomplete assessment dates for tumor assessment

All investigation dates (e.g. peripheral blood, bone marrow) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. peripheral blood, bone marrow) if the overall disease response at that assessment is CR/CRi/UNK. Otherwise, if overall lesion response is relapsed disease or no response, the assessment date is calculated as the earliest date of all investigation dates at that evaluation number that reveals a relapse/no response. If all measurement dates have no day recorded, the first of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.6.5 Incomplete date for relapse or last known date subject in remission

The "Remission/Relapse Information" eCRF will be used to track the relapse status for those patients who enter the secondary follow-up phase while in remission.

If the day or month of date of relapse or last known date subject in remission is missing, it will be imputed to the minimal of date of assessment and the following:

- Missing day: 15th day of the month and year
- Missing day and month: 01-Jul of the year

5.6.6 Incomplete date for death or last known date subject alive

If the day or month of death is missing from the death eCRF, death will be imputed to the maximum of the full (non-imputed) last contact date and the following:

- Missing day: 15th day of the month and year of death
- Missing day and month: 01-Jul of the year of death

If the day or month of last known date subject alive is missing in the survival eCRF, it will be first imputed with the following:

- Missing day: minimum of the date of assessment and 15th day of the month and year of last known date subject alive
- Missing day and month: minimum of the date of assessment and 01-Jul of the year of last known date subject alive

Then the above imputed last know date subject alive will be used to calculate the last contact date.

5.6.7 Incomplete date for initial diagnosis, first relapse and most recent relapse

If the day or month of initial diagnosis, first relapse or most recent relapse is missing, the date of initial diagnosis will be imputed to the minimum of the informed consent date -1 and the following:

- Missing day: 15th day of the month and year
- Missing day and month: 01-Jul of the year

5.6.8 Date of hospitalization imputation

Missing hospitalization end date or end date after the analysis data cutoff will be imputed following the same conventions as for AE end date imputation.

5.7 Determination of missing scheduled disease assessments

For some time-to-event endpoints (i.e. DOR, RFS, EFS), classification of censoring or event can depend on the number of missing scheduled disease assessments.

The protocol defined schedule of disease assessments is every month for the first 6 months, every 3 months thereafter until Month 24, and every 6 months thereafter until Month 52. Each assessment is expected to be performed at the scheduled time point plus or minus 2 weeks in general, i.e. the window is 4 weeks or 1 month.

An event is considered as after 2 or more missing scheduled disease assessments if the distance between the last adequate non-relapse assessment and the event is larger than the threshold, defined as two times the protocol specified interval between the disease assessments plus the protocol allowed window around the assessments.

More specifically, an event is considered as having occurred after 2 or more missing scheduled disease assessments if the distance between the last adequate non-relapse assessment and the event is:

- > 91 days (i.e. 1+1+1 months), if the last adequate non-relapse assessment occurs on or before Day 136 (i.e. middle point of Month 4 and Month 5)
- > 152 days (i.e. 1+3+1 months), if the last adequate non-relapse assessment occurs after Day 136 and on or before Day 167 (i.e. middle point of Month 5 and Month 6)
- > 213 days (i.e. 3+3+1 months), if the last adequate non-relapse assessment occurs after Day 167 and or on before Day 593 (i.e. middle point of Month 18 and Month 21)
- > 304 days (i.e. 3+6+1 months), if the last adequate non-relapse assessment occurs after Day 593 and on or before Day 684 (i.e. middle point of Month 21 and Month 24)
- > 395 days (i.e. 6+6+1 months), if the last adequate non-relapse assessment occurs after Day 684

5.8 CNS disease history search

CNS disease history is defined by the following MedDRA terms as collected in medical history:

- Neurological disorders congenital (HLGT)
- Congenital and peripartum neurological conditions (HLGT)
- Central nervous system haemorrhanges and cerebrovascular accidents (HLT)
- Noninfectious encephalopathy/delirium (SMQ) (broad)

5.9 Rule of exclusion criteria of analysis sets

Table 5-9 Major protocol deviations

Protocol ID[1]	Deviation ID[2]	Description of Deviation	Exclusion from Analyses
INCL01	INCL01	No confirmation that patient is Relapsed or refractory pediatric B-cell ALL defined by inclusion criteria	Excluded from PP analysis
INCL02	INCL03	CD19+ Tumor expression not demonstrated	Excluded from PP analysis
EXCL01	EXCL01	Patient has isolated extra-medullary disease relapse at study entry	Excluded from PP analysis
EXCL03	EXCL03	Patient has Burkitt's lymphoma/leukemia at study entry	Excluded from PP analysis
EXCL06	EXCL06	Patient had treatment with prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy per exclusion criteria at study entry	Excluded from PP analysis
NA	TRT01	CTL019 T cells were not prepared, stored, transported and/or administered to the patient according to protocol	Excluded from PP analysis
NA	TRT02	CTL019 T-cells released from the manufacturing facility without meeting all approved release criteria, and patient was infused or was not released through exceptional release and patient was infused	Excluded from PP analysis

Protocol ID[1]	Deviation ID[2]	Description of Deviation	Exclusion from Analyses
NA	TRT03	Patient not dosed according to protocol	Excluded from PP analysis
NA	OTH01	Missing or incomplete documentation of disease at baseline	Excluded from PP analysis

[1] based on protocol version 04

[2] based on data review plan version 06

6 References

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