NOVARTIS

Clinical Development

CTL019 / tisagenlecleucel / Kymriah®

CCTL019C2202 / NCT03610724

A Phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in pediatric patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL) (BIANCA)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous version

Date	Version number	Summary of changes
08-Mar-2019	1.0	First version
06-Jan-2020	2.0	- Updates to align with Protocol Amendment 1.0 • Patients aged up to 25 years can now enroll in the study • Patients with Burkitt leukemia can now enroll in the study • Some other minor updates to align with protocol - Updated Biomarker analyses (Section 2.10) to align with data collected in RaveX studies. (Previous text had been based on OCDC studies). - Added time windows for PK, immunogenicity, biomarker, growth and Tanner staging analyses (Section 6.4) - Moved some text regarding CRS analyses from Section 2.8.6 to Section 2.8.2.1.1 - Removed requirement to list all laboratory values. Only abnormal laboratory values will be listed (Section 2.8.4)
17-Nov-2021	3.0	- Updates to assess the impact of the COVID-19 pandemic (added Section 2.10) - Added reason for SAP amendment (Section 1.3). • All analyses related to FL are deleted. • Adaptions on secondary endpoint analyses (DOR and RFS) with small subgroups due to low number of responders. - Minor extensions or adaptions on definitions and explanations.
17-May-2023	4.0	This amendment occurs after the primary analysis has been performed and therefore this amendment only concerns the final analysis to be peformed after LPLV. Updates are related to the following topics: - Reasons for changes related to SAP amendment 2 deleted from Section 1 (Introduction).

Date	Version number	Summary of changes
		- Output presentation by histology instead of age group (in Section 2.3, 2.4 and 2.8) - Tables based on EAS added for Section 2.3.2, 2.3.5 and 2.4.2 - Prior/Post antineoplastic therapies are only presented by preferred term (Section 2.4.2) - Minor wording updates of subgroup analyses for primary endpoint to harmonize with CSR TFL shells (Section 2.5.5) - Sensitivity analyses – without censoring for HSCT – added for EFS and PFS (Section 2.7.2.2 and 2.7.2.4) - New AE/AESI tables added to cover relationship to tisagenlecleucel (Section 2.8.2) - CRS episode with maximum grade is analyzed instead of first CRS episode (Section 2.8.2.1.1) - T1/2 deleted from PK parameter analysis (Section 2.9) - Update of biomarker analysis to harmonize with CSR TFL shells (Section 2.8.6 and 2.11.1) - Minor wording updates in almost all SAP Sections

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ATC	anatomical therapeutic classification
AUC	area under the curve
BL	Burkitt lymphoma/leukemia
BOR	best overall response
CAR	chimeric antigen receptor
CI	confidence interval
CKAS	cellular kinetic analysis set
CR	complete response
CRS	cytokine release syndrome
CSF	clinical service form
CSR	clinical study report
CT	computerized tomography
CTC	common toxicity criteria
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DD	drug dictionary
DLBCL	diffuse large b-cell lymphoma
DMC	Data Monitoring Committee
DOR	duration of response
EAS	efficacy analysis set
eCRF	electronic case report form
EFS	event-free survival
EMA	European Medicines Agency
EOS	end of study
FAS	full analysis set
FDA	Food and Drug Administration
FL	follicular lymphoma
GZL	gray zone lymphoma
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
ICU	intensive care unit
IL	interleukin
i.v.	intravenous
KM	Kaplan-Meier
LD	lymphodepleting
LLOQ	lower limit of quantitation
LPLV	Last patient last visit
MedDRA	medical dictionary for regulatory activities
mg	milligram(s)
MR	minor response

MRI	magnetic resonance imaging
NHL	non-Hodgkin lymphoma
NR	no response
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PT	preferred term
qPCR	quantitative polymerase chain reaction
RCL	replication competent lentivirus
RFS	relapse-free survival
r/r	relapsed or refractory
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
[redacted]	[redacted]
ULOQ	upper limit of quantification
UNK	unknown
WBC	white blood cell
WHO	World Health Organization
WOC	withdrawal of consent

1 Introduction

This document describes the detailed statistical methodology for the study CCTL019C2202 (BIANCA): a Phase II, single arm, multicenter, open label study to determine the safety and efficacy of tisagenlecleucel in pediatric and young adult subjects with CD19+ relapsed or refractory (r/r) mature B-cell non-Hodgkin lymphoma (NHL).

Up to two clinical study reports (CSRs) could result from this SAP:

- Primary analysis: Perfomed after about 26 subjects with r/r B-cell NHL and measureable disease at baseline have been infused and followed for at least 6 months or discontinued earlier, as well as at least 50% of those subjects have been followed for at least 9 months.
- Final analysis: Will be performed after all subjects have finished the study.

The content of this Statistical Analysis Plan (SAP) is based on protocol CCTL019C2202 version 01 (Amended Protocol).

The changes in this SAP amendment only pertain to the final analysis. The primary analysis was performed using the previous version of this SAP (amendment 2). All decisions regarding the final analysis, as defined in this SAP document, have been made prior to the final database lock of the study data.

1.1 Study design

This study will have the following sequential phases for all subjects:

- Consent
- Screening
  - Leukapheresis collection
- Pre-treatment
  - Tisagenlecleucel manufacturing
  - Optional bridging chemotherapy
  - Lymphodepleting (LD) chemotherapy (as applicable)
- Treatment and follow-up

Screening begins after signing the study Informed Consent Form (ICF). Leukapheresis (CD3 cell collection) can begin after signing the ICF, or at any time before screening if this is the SOP at treatment centers which provided the cells meet the specifications for manufacture according to protocol. Final enrollment is defined as the point at which a subject meets all inclusion/exclusion criteria and the subject's leukapheresis material is received and accepted for manufacturing.

The **pre-treatment** phase will begin at enrollment until Day -1 (pre-infusion visit) and includes the manufacturing of tisagenlecleucel. Tisagenlecleucel cell product will be prepared and released by the manufacturing facility to the study site approximately 4-6 weeks after manufacturing has commenced, provided all required safety and quality release criteria have been met. This phase may also include bridging therapy of the investigator's choice (if needed this may be continued from screening through the pre-treatment phase), and LD chemotherapy, which is completed 2 to 14 days before the tisagenlecleucel infusion.

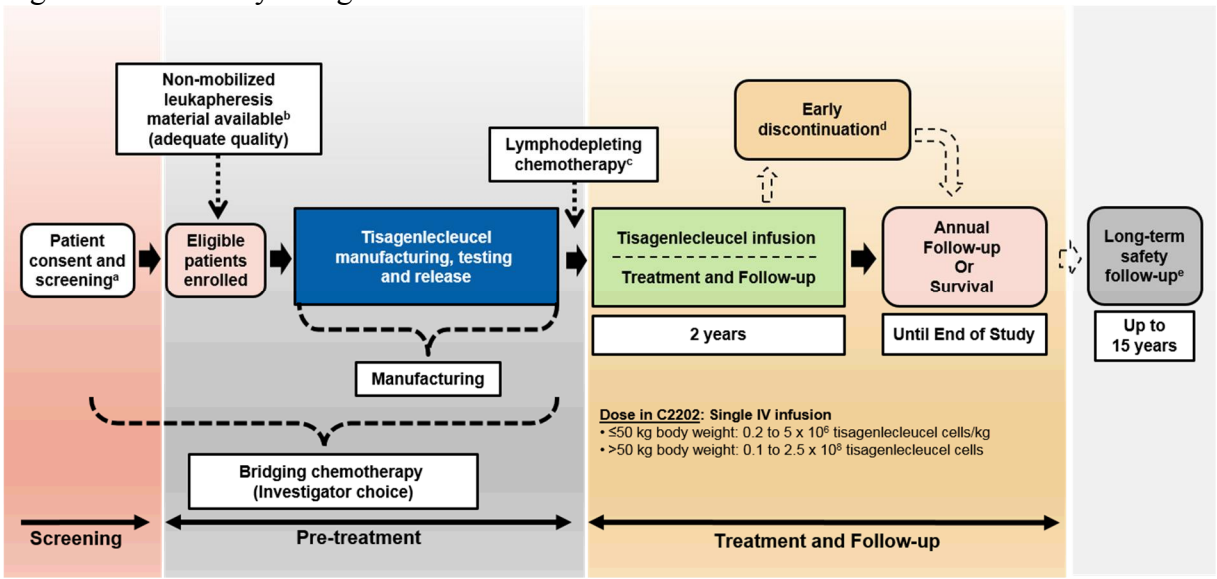
The **treatment and follow-up phase** starts with tisagenlecleucel infusion (Day 1). The infused subjects will then be followed for disease status, pharmacokinetics (PK), biomarker, safety and survival according to the assessment schedule defined in study protocol Table 8-1 until **end of study (EOS)**, which is defined as when all subjects complete the 2-year post-treatment assessments or discontinue early.

The investigational treatment is a single infusion of 0.2 to 5 $x10^6$ chimeric antigen receptor (CAR)-positive viable T cells per kilogram of body weight (subjects ≤50 kg) or 0.1 to 2.5 $x10^8$ CAR-positive viable T cells (subjects >50 kg) via an intravenous infusion. Subjects will be infused with the maximum cell dose within this range that can be individually manufactured.

Efficacy will be evaluated by the investigator using computerized tomography/magnetic resonance imaging (CT/MRI) and positron emission tomography (PET)-CT or PET-MRI based on International Pediatric NHL Response Criteria [Sandlund et al 2015] clarified by Novartis for pediatric population as outlined in the Protocol Appendix 1. Baseline disease assessment will be performed locally, at screening and repeated within two weeks prior to infusion. Efficacy will be assessed at day 28, months 3, 6, 9, 12, 18, 24 and then every 12 months until relapse, disease progression, death, loss to follow-up, withdrawal of consent (WOC) or EOS.

A post-study long-term follow-up for tisagenlecleucel safety will continue under a separate destination protocol [CCTL019A2205B].

Figure 1-1 Study Design



[a] Aggressive B-cell NHL subtypes (BL, DLBCL, PMBCL, GZL), in addition FL subjects may also be treated; age ≤25 years; r/r to one or more lines of prior therapies

[b] Previous leukapheresis collection or during screening

[c] Administered as applicable, fludarabine (30 mg/m^2 i.v. daily for 4 days) and cyclophosphamide (500 mg/m^2 i.v. daily for 2 days starting with the first dose of fludarabine)

[d] Subjects that discontinue early, post-infusion prior to M24 visit, will continue in annual follow-up until EOS (until all subjects who receive tisagenlecleucel complete 2 years of post-treatment phase or discontinue early).

[e] Conducted under a separate destination protocol

1.2 Study objectives and endpoints

A full list of study objectives and related endpoints are provided in Table 1-1 and detailed in the study protocol.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints	Section
Primary Objective	**Endpoints for primary objective**	
Evaluate the efficacy of tisagenlecleucel therapy as measured by ORR and determined by local investigator assessments in subjects with aggressive r/r B-cell NHL	ORR includes complete response (CR) and partial response (PR) determined by local investigator assessments.	Section 2.5
Secondary Objectives	**Endpoints for secondary objectives**	
Evaluate the duration of response (DOR) in subjects with aggressive r/r B-cell NHL	DOR is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented progression or death due to underlying cancer.	Section 2.7.2.1
Evaluate event free survival (EFS) in subjects with aggressive r/r B-cell NHL	EFS is defined as the time from date of first tisagenlecleucel infusion to the earliest date of death from any cause, disease progression as determined by local investigator assessments, or starting new anticancer therapy for underlying cancer, excluding HSCT.	Section 2.7.2.2
Evaluate relapse free survival (RFS) in subjects with aggressive r/r B-cell NHL	RFS is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented disease progression or death due to any cause.	Section 2.7.2.3
Evaluate progression free survival (PFS) in subjects with aggressive r/r B-cell NHL	PFS is defined as the time from the date of first tisagenlecleucel infusion to the date of first documented disease progression as determined by local investigator assessments or death due to any cause	Section 2.7.2.4
Evaluate overall survival (OS) in subjects with aggressive r/r B-cell NHL	OS is defined as the time from date of first tisagenlecleucel infusion to the date of death due to any cause.	Section 2.7.2.5
Evaluate the safety of tisagenlecleucel therapy	Physical examination, vital signs, adverse events, laboratory abnormalities, performance status and as applicable physical development	Section 2.8
Characterize the in vivo cellular kinetics (levels, expansion, persistence) of tisagenlecleucel cells into target tissues (blood, bone marrow, lymph nodes, cerebral spinal fluid and other tissues if available), as measured by qPCR in relation to safety and efficacy	Cellular kinetics parameters: Cmax, Tmax, AUCs, Clast, Tlast, and/or other relevant parameters in peripheral blood, bone marrow, lymph nodes, cerebrospinal fluid and other tissues as appropriate, Month 3 (±14 days) response, safety endpoint (CRS grade).	Section 2.9
Characterize the presence of pre-existing and treatment induced immunogenicity and impact on cellular kinetics and response	Levels of pre-existing and treatment induced immunogenicity, cellular kinetic parameters, and efficacy (Month 3 (±14 days) response)	Section 2.9.1
Assess the proportion of subjects who proceed to transplant post-tisagenlecleucel therapy until EOS	Number of subjects that proceed to HSCT after tisagenlecleucel infusion until EOS will be described	Section 2.8.5

Objectives	Endpoints	Section
Retrospective assessment of potential CRS predictive models considering also data from other CTL019 trials	Assess the ability for early prediction of cytokine release syndrome utilizing clinical and biomarker data	Section 2.8.6

[redacted]

2 Statistical methods

All analyses will be performed by Novartis Oncology Biostatistics and Statistical Programming personnel or designated CRO according to the data analysis described in the following sections. SAS version 9.4 and R version 3.5.3 (or later version if available at time of database lock) will be used for the analysis.

Data included in the analysis

The majority of infused subjects with mature r/r NHL ≤ 25 years old will have an aggressive subtype: Burkitt lymphoma/leukemia (BL), diffuse large B-Cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) or gray zone lymphoma (GZL). Due to the rarity of

follicular lymphoma (FL) in the pediatric population, no subjects with this indolent subtype were enrolled in the study.

2.1 Data analysis general information

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to the expected small number of subjects enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e., mean, standard deviation (SD), median, q1, q3, minimum, and maximum).

2.1.1 General definitions

2.1.1.1 Treatment strategy

The **tisagenlecleucel treatment strategy** includes an optional LD chemotherapy and/or a bridging chemotherapy followed by a tisagenlecleucel infusion. Per protocol, subjects may only receive one infusion of tisagenlecleucel.

Study treatment includes all the components of the treatment strategy as defined above, whereas **study drug** refers to tisagenlecleucel.

2.1.1.2 Completion of treatment strategy

The tisagenlecleucel treatment strategy is considered completed when the subject is infused with tisagenlecleucel. Subjects are considered discontinued from the tisagenlecleucel treatment strategy if subjects discontinue the study without tisagenlecleucel infusion.

2.1.1.3 Study day

The study day describes the day of the event or assessment date relative to the date of tisagenlecleucel infusion (reference start date). The study day is defined as:

- (date of the event/assessment − date of tisagenlecleucel infusion + 1), if event is on or after the date of tisagenlecleucel infusion;
- date of the event/assessment − date of tisagenlecleucel infusion), if event precedes the date of tisagenlecleucel infusion. In this case, the study day will be negative.

The study day will be displayed in the data listings.

2.1.1.4 Baseline

For **baseline disease evaluations**, the last assessment (bone marrow, blood count, clinical service form [CSF], physical exam, etc.) after bridging therapy and prior to tisagenlecleucel

infusion will be used as baseline. Any imaging assessment obtained after infusion cannot be considered baseline/pre-infusion images.

For **safety evaluations** (i.e. laboratory and vital signs), the last available assessment before tisagenlecleucel infusion is taken as 'baseline' value.

For not infused subjects the last available assessment is used as baseline.

If subjects have no value as defined above, the baseline result will be missing.

2.1.1.5 Duration of study follow-up

The study follow-up duration is defined as: min (Cut-off date, Date of study completion or discontinuation from study follow-up) – Tisagenlecleucel infusion date + 1)/30.4375. The study follow-up time will be calculated and summarized.

2.1.1.6 Last contact date

The last contact date will be used for censoring of subjects in the analysis of overall survival (OS).

For subjects 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 was true contact with the subject.

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 subject was known to be alive from Survival Follow-up page	No condition
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose.
Any specific efficacy assessment date if available	Evaluation is not missing.
Laboratory/PK 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. Imputation of partial dates is allowed to be used for event (death) and for censoring date only if coming from the survival follow-up electronic case report form (eCRF) page (see Section 6.1.2.1).

2.1.1.7 Lost to follow-up

For OS analysis, subjects will be considered as lost to follow-up if the time between their last contact date and the analysis cut-off date is greater than or equal to 105 days (i.e., 3 months plus 2 weeks, assuming 1 month = 30.4375 days).

For response related time-to-event analyses (i.e. duration of response [DOR], relapse-free survival [RFS] and event-free survival [EFS]), subjects will be considered as lost to follow-up if the subject discontinued the study due to loss to follow-up.

2.2 Analysis sets

2.2.1 Screened set

The screened set comprises all subjects who have signed the ICF and were screened in the study.

2.2.2 Enrolled set

The enrolled set comprises all subjects who are enrolled in this study. Enrollment is defined as the point at which the subject meets all inclusion/exclusion criteria, and the subject's leukapheresis material is received and accepted for manufacturing. Once a subject is enrolled, he/she will remain in the enrolled set, even if the subject does not actually meet all inclusion/exclusion criteria.

2.2.3 Efficacy analysis set

The efficacy analysis set (EAS) includes all subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel and had measurable disease at baseline.

The EAS will be used as the main analysis set for efficacy.

2.2.4 Full analysis set

The full analysis set (FAS) comprises all subjects who received an infusion of tisagenlecleucel.

2.2.5 Safety set

The safety set comprises all subjects who received an infusion of tisagenlecleucel. The safety set is the same as the FAS, and is the main analysis set for safety.

2.2.6 Cellular kinetic analysis set

The tisagenlecleucel cellular kinetic analysis set (CKAS) consists of subjects in the FAS who provide an evaluable cellular kinetic profile (at least one valid cellular kinetic concentration). The CKAS will be used for summaries (tables and figures) of cellular kinetic data. The FAS will be used for listings of cellular kinetic data.

Note that subjects may be removed from the estimation of certain cellular kinetic parameters on an individual basis depending on the number of available samples. These subjects will be identified at the time of the analyses.

[redacted]

2.3 Subject disposition, demographics and other baseline characteristics

Unless specified otherwise, the FAS will be used for all baseline and demographic summaries and listings. The summaries will be displayed by histology: Burkitt lymphoma (BL) and large B-cell lymphoma (LBCL), as well as all subjects.

2.3.1 Subject Disposition

Subject disposition will be summarized as follows:

- Screening disposition for the screened set
- Treatment disposition for enrolled set
- Study disposition post infusion for the full analysis set

For each disposition, subjects status including completed, ongoing or discontinued with reason for discontinuation will be summarized based on the number and percentage of subjects as listed on the disposition eCRF pages.

Study follow-up will be summarized numerically (in months) as well as by categories: <6 months, 6 months to <12 months, 12 months to <24 months and ≥24 months.

All disposition data will be listed using the screened set.

2.3.2 Analysis sets

The number (%) of subjects in each analysis set will be summarized (using the screened set as denominator). In addition, listings of subjects excluded from the analysis sets will be provided.

2.3.3 Basic demographic and background data

Demographic and baseline disease characteristics data will be summarized on the FAS and listed on the enrolled set. The summary table will be additionally presented on the EAS.

The following grouping will be applied:

- Karnofsky/Lansky performance status: 100-80, 70-50, <50.

Additionally the demographic variables age (years), sex, race, ethnicity and weight for manufacturing (kg) will be displayed.

2.3.4 Medical history

Medical history and on-going conditions, including cancer-related conditions and symptoms entered on the eCRF will be summarized and/or listed for the FAS. The summaries will be presented by primary system organ class (SOC), preferred term (PT). Counts and percentages will be displayed separately for all subjects. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

2.3.5 Diagnosis and extent of cancer

Diagnosis and extent of cancer will be summarized on the FAS and listed on the enrolled set. The summary table will be additionally presented on the EAS.

Summary statistics will be displayed for the following continuous variables:

- Age at initial diagnosis (years)
- Time since initial diagnosis to first recurrence/progression (months)
- Time since initial diagnosis to most recent relapse/progression (months)

In addition, the following categorizations of continuous variables will be done:

- Age at initial diagnosis (years) (<5, 5-14, 15-17, ≥18)

Numbers (%) will be presented for the following categorical variables:

- Diagnosis of disease/ Predominant histology
- Stage at initial diagnosis
- Stage at time of study entry
- Bone marrow involved at study entry
- Any extralymphatic sites involved by lymphoma at study entry
- Disease status

Time from initial diagnosis of primary site to start of tisagenlecleucel infusion and time since most recent recurrence/relapse progression to tisagenlecleucel infusion are presented separately using descriptive statistics.

2.3.6 Protocol deviations

The number (%) of subjects in the FAS who have at least one confirmed protocol deviation will be tabulated by deviation category (as specified in the study Data Quality Plan). All protocol deviations will be listed based on the enrolled set.

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

2.4.1 Study treatment / compliance

Summaries on study treatment and compliance will be done on the safety set. They will be displayed by histology: Burkitt lymphoma (BL) and large B-cell lymphoma (LBCL), as well as all subjects.

Tisagenlecleucel

The total CAR-positive viable T cells count infused (10^8 cells, for subjects >50kg), the total weight-adjusted CAR-positive viable T cells count infused (10^6/kg, for subjects ≤50kg) and

the total viable cell count infused (10^8 cells, for all subjects) will be summarized using descriptive statistics. The derivation of the total CAR-positive viable T cell count infused is detailed in Appendix Section 7.3.
Additionally subjects will be categorized as below, within or above the target dose ranges:

- 0.2 to 5.0 x10^6 CAR-positive viable T cells per kg body weight (subjects ≤50kg),
- 0.1 to 2.5 x10^8 CAR-positive viable T cells (subjects >50kg).

All exposure data will be listed.

Time from screening and enrollment to tisagenlecleucel infusion will be summarized using descriptive statistics.

Bridging/Lymphodepleting (LD) chemotherapy

Number and percentage of subjects receiving bridging/LD chemotherapies will be summarized by the type of therapy (i.e., fludarabine/cyclophosphamide bridging/LD chemotherapy, cytarabine/etoposide bridging/LD chemotherapy and no bridging/LD therapy). Duration of exposure and reason for therapy discontinuation will also be displayed. All summary tables are based on the enrolled set and displayed by histology: Burkitt lymphoma (BL) and large B-cell lymphoma (LBCL), as well as all subjects.

Bridging/LD chemotherapies received after enrollmentwill be listed.

2.4.2 Prior, concomitant and post therapies

Unless specified otherwise, the FAS will be used for all prior, concomitant and post tisagenlecleucel infusion therapy summaries and listings. The summaries will be displayed by histology: Burkitt lymphoma (BL) and Large B-cell lymphoma (LBCL), as well as for all subjects.

Prior and concomitant medications

Prior medications are defined as all medications starting and ending prior to the date of tisagenlecleucel infusion.Concomitant therapy is defined as all interventions (therapeutic treatments and procedures)
given to a subject during the study other than those specified as study treatment. Concomitant therapy includes medications (other than tisagenlecleucel infusion, lymphodepleting or bridging chemotherapies) starting on or after the date tisagenlecleucel infusion or medications starting prior to the date of tisagenlecleucel infusion and continuing after the date of tisagenlecleucel infusion. Prior and post antineoplastic medications/therapies are presented separately and thus are not included in the summary of concomitant medications.
Prior and concomitant medications will be coded using the WHO Drug Reference Listing dictionary that employs the WHO ATC classification system and summarized by lowest ATC and PT using frequency counts and percentages. Medical procedures will be coded using MedDRA and summarized by SOC and PT. The safety set will be used for all concomitant medication summaries. Listings will be based on the enrolled set.

Transfusions during the study will be listed using the enrolled set.

Anti-cytokine medications are given for severe cytokine release syndrome (CRS) due to tisagenlecleucel cells. The number and percentage of subjects requiring anti-cytokine medications for the management of CRS will be summarized. The frequency and dose of rescue medications will also be summarized by PT.

Prior enrollment anti-cancer therapy

The number and percentage of subjects who received any prior antineoplastic medication, prior antineoplastic radiotherapy, prior hematopoietic stem cell transplant (HSCT) or prior antineoplastic surgery will be summarized. Prior antineoplastic medications will be summarized by PT. Separate listings will be produced for prior antineoplastic medications, radiotherapies, hematopoietic stem cell transplants (HSCT) and surgeries.

Antineoplastic medications will be coded using the World Health Organisation (WHO) Drug Dictionary (DD); antineoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS. Additional summary tables will be based on the EAS

Post treatment anti-cancer therapy

The number and percentage of subjects with antineoplastic therapies post tisagenlecleucel infusion will be summarized by PT, using the FAS. In addition post hematopoietic stem cell transplants (HSCT) will be tabulated. Separate listings will be displayed for post hematopoietic stem cell transplants (HSCT), post antineoplastic medications, post antineoplastic radiotherapies and post antineoplastic surgeries.

2.5 Analysis of the primary objective

The primary objective of the study is to evaluate the efficacy of tisagenlecleucel therapy as measured by ORR, which includes complete response (CR) and partial response (PR) based on local investigator assessments in subjects with aggressive r/r B-cell NHL who have measurable disease at baseline (baseline assessment prior to infusion for subjects on bridging therapy should be done after completion of bridging therapy).

2.5.1 Primary endpoint

The primary endpoint is ORR as determined by local investigator assessment in subjects with aggressive r/r B-cell NHL. The ORR is defined as the proportion of subjects with a best overall response (BOR) of CR or PR, where the BOR is defined as the best disease response recorded from tisagenlecleucel infusion until progressive disease (PD) or start of new anticancer therapy (including HSCT), whichever comes first. The primary endpoint analysis will be performed on EAS comprising aggressive r/r B-cell NHL subjects. The overall response assessment is based on International Pediatric NHL classification response criteria [Sandlund et al 2015].

A subject will have a BOR of CR if they had CR, as overall disease response for at least one of the assessments.

A subject will have a BOR of PR if at least one overall response of PR is available (and the subject would not qualify for CR).

A subject will have a BOR of MR if at least one overall disease response of MR is available (and the subject does not qualify for CR or PR).

A BOR of NR will be declared when at least one NR assessment is available earliest at 4 weeks after tisagenlecleucel infusion (and the subject would not qualify for CR, PR or MR).

A subject will have a BOR of PD if the PD was observed less than 28 weeks after tisagenlecleucel infusion (and the subject does not qualify for CR, PR, MR or NR).

If a subject does not qualify for CR, PR, MR, NR or PD, then their BOR will be Unknown (UNK).

See Study Protocol Appendix 1 for details of disease response criteria.

2.5.2 Statistical hypothesis, model, and method of analysis

The ORR along with the 95% exact Clopper-Pearson confidence intervals (CI) will be summarized in subjects with aggressive r/r B-cell NHL in the EAS.

2.5.3 Handling of missing values/censoring/discontinuations

Subjects in this study who are of unknown clinical response will be treated as non-responders.

2.5.4 Supportive analyses

The primary analysis will also be performed on the enrolled set and the FAS. Additionally, if there are subjects outside the target dose range, the primary analysis will be performed on this subgroup as well using the same methodology.

2.5.5 Subgroup analyses for the primary endpoint

Subgroup analyses of the primary endpoint will be performed on the following based on the subject's baseline status using the EAS:

- Age: <18 years, ≥18 years (further age subgroups may be considered depending on the ages of patients enrolled)
- Gender: male, female
- Race: White, Asian, Black, Other
- Ethnicity: Hispanic or Latino, Other
- Disease subtypes: BL, DLBCL, other
- Prior response status: Primary refractory/Refractory or Relapsed/Progression
- Use of prior rituximab: Yes or No
- Stage of disease at baseline: I/II or III/IV
- Tumor mass at baseline: LDH > ULN or LDH <= ULN
- Autologous HSCT before infusion: Yes or No
- Surgery before infusion: Yes or No

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

2.6 Analysis of the key secondary objective

Not applicable. No formal hypothesis testing is planned.

2.7 Analysis of secondary efficacy objectives

2.7.1 Secondary objectives

The secondary objectives in this study include evaluating DOR, EFS, RFS, PFS, OS and safety. DOR, EFS, RFS, PFS and OS will be analyzed in subjects with aggressive r/r B-cell NHL. Kaplan-Meier (KM) analyses will be performed if at least one event is observed. Local investigator assessment will be used for secondary endpoints that involve disease response.

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 Duration of response (DOR)

DOR applies only to subjects whose BOR was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) whichever occurs first, to the date of first documented relapse or death due to underlying cancer (at time of primary endpoint analysis).

In case a subject does not have progression or death due to underlying cancer prior to data cut-off, DOR will be censored at the date of the last adequate response assessment, i.e. the last date where the overall disease response is not missing or unknown, on or prior to the earliest censoring event. The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling HSCT)

Distribution of DOR may be estimated using the KM method in which death due to reason other than underlying cancer will be censored. In case only a small number of subjects are observed with BOR CR or PR the DOR will only be analyzed descriptively.

As HSCT is an important treatment option in responding subjects, it is appropriate to consider the date of HSCT as 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 underlying cancer) after HSCT will be used for the calculation of DOR.

2.7.2.2 Event free survival (EFS)

EFS is the time from date of first tisagenlecleucel infusion to the earliest date of the following:

- Death from any cause
- Disease progression as determined by local investigator assessments

- New anticancer therapy for underlying cancer, excluding HSCT (at time of primary endpoint analysis)

In case a subject does not have any of the above events prior to data cut-off, EFS is censored at the last adequate response assessment date, i.e. the last date where the overall disease response is not missing or unknown, 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
- HSCT (see below for handling of HSCT)

Subjects who proceed to HSCT after tisagenlecleucel infusion will be censored at the time of HSCT.

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

In addition a sensitivity analysis will be performed using the same methodology but excluding HSCT as a censoring reason.

2.7.2.3 Relapse free survival (RFS)

RFS applies only to subjects whose BOR was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) whichever occurs first, to the date of first documented relapse or death due to any cause (at time of primary endpoint analysis).

In case a subject does not have progression or death due to any cause prior to data cut-off, RFS will be censored at the date of the last adequate response assessment, i.e. the last date where the overall disease response is not missing or unknown, on or prior to the earliest censoring event. The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (see below for handling HSCT)

Subjects who proceed to HSCT after tisagenlecleucel infusion will be censored at the time of HSCT.

RFS will be assessed only in subjects with the BOR of CR or PR. The distribution function of RFS may be estimated using the KM method. In case only a small number of subjects are observed with BOR CR or PR the RFS will only be analyzed descriptively.

The median RFS along with 95% CI will be presented if appropriate.

In addition a sensitivity analysis will be performed using the same methodology but excluding HSCT as a censoring reason.

2.7.2.4 Progression free survival (PFS)

PFS is defined as the time from the date of first tisagenlecleucel infusion to the date of event defined as the first documented progression as determined by local investigator assessment or death due to any cause (at time of primary endpoint analysis). If a subject has not had an event, PFS is censored at the date of the last adequate assessment.

In case a subject does not have progression or death prior to data cut-off, PFS will be censored at the date of the last adequate response assessment, i.e. the last date where the overall disease response is not missing or unknown, on or prior to the earliest censoring event. The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (see below for handling of HSCT)

Subjects who proceed to HSCT after tisagenlecleucel infusion will be censored at the time of HSCT.

PFS will be estimated using the KM method and the median PFS as well as proportion of subjects without event at 3, 6, 9, and 12 months post tisagenlecleucel infusion will be presented along with 95% CI.

In addition a sensitivity analysis will be performed using the same methodology but excluding HSCT as a censoring reason.

2.7.2.5 Overall survival (OS)

OS is the time from date of first tisagenlecleucel infusion to the date of death due to any cause (at time of primary endpoint analysis).

In case a subject not known to have died at the data cut-off date is censored at his/her last contact date, which is defined as the latest date they were known to be alive. The censoring reason could be:

- Ongoing without event
- Lost to follow-up, i.e. subjects will be considered as lost to follow-up if the time between their last contact date and the analysis cut-off date is greater than or equal to 105 days.

Subjects will be followed for survival also in case of HSCT.

As a sensitivity analysis OS will be summarized censoring for HSCTusing the same methodology as for the DOR, EFS, RFS and PFS analysis.

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

A summary of censoring reasons as well as a summary of follow-up time for OS as well as DOR, EFS, RFS and PFS will be given.

2.8 Safety analyses

The main focus of the safety analyses is to evaluate the safety post tisagenlecleucel infusion. All safety analyses will be based on the safety set - unless otherwise specified.

All summaries – unless otherwise specified - will be displayed by histology: Burkitt lymphoma (BL) and large B-cell lymphoma (LBCL), as well as all subjects.

2.8.1 Analysis set and reporting periods

Table 2-2 summarizes the mutually exclusive safety reporting periods as well as the subjects to be included in each of the segments.

Note that the **post-infusion period** will be the main period of safety reporting.

Table 2-2 Safety reporting periods

Period	Definition	Subjects to be included, Analysis Set
Pre-LD period	From the day of subject's informed consent to the day before the first LD chemotherapy dose or the day before infusion of tisagenlecleucel if the LD chemotherapy is not given	Screened subjects Screened set
LD period (note: this period only applies to subjects who receive LD chemotherapy)	From the first day of LD chemotherapy • to the day before infusion of tisagenlecleucel, for subjects who receive infusion, or • to the earlier of date of discontinuation or 30 days after last dose of LD chemotherapy for subjects who do not receive infusion of tisagenlecleucel	All subjects who received LD chemotherapy
Post-infusion period	Starting at day of first tisagenlecleucel infusion until EOS	All subjects who received an infusion of tisagenlecleucel, Safety set

Abbreviations: EOS=end of study; LD=lymphodepleting

2.8.2 Adverse events

The adverse events (AE) reporting follows a modified safety reporting rule as described in Protocol Appendix 3.

Reporting of AEs (except for CRS) will be based on MedDRA (latest version per database lock) and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The grading of CRS will be based on protocol specific grading scales (Protocol Section 6.6.2.1).

For the summary of safety post-tisagenlecleucel infusion, AE summaries will include all AEs that started or worsened during the post-infusion period, i.e. defined as **tisagenlecleucel-treatment-emergent** AEs. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by relation to study drug, primary SOC, PT and severity (based on grades as described above).

AEs will be summarized by number and percentage of subjects having at least one AE in each primary SOC and for each PT using MedDRA coding. A subject with multiple occurrences of

an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event.

The AE summary tables will be presented by timing (Any time, within 8 weeks, >8 weeks to 1 year, 1 year to 2 years post tisagenlecleucel infusion, and after this in 1-yearly intervals): A subject with multiple grades for the same PT or primary SOC within a time interval will only be counted with the maximum grade, a subject with multiple AEs (independent of primary SOC or PT) will only be counted with the maximum grade in the 'Number of subjects with at least one event' row. The percentage for the summary of >8 weeks to year and >1 year post tisagenlecleucel infusion will be based on the number of subjects who are still in study follow-up at that time.

AEs with missing CTCAE grade will be included in the ‘all grades’ column of the summary tables. The frequency of AEs of grade 3 or above will be summarized together.

In AE summary tables, the primary SOC will be presented alphabetically and PT will be sorted within the primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the ‘all grades’ column.

For the **safety post tisagenlecleucel infusion**, the following AE summaries will be produced on post-infusion period:

- Overview of AEs, deaths, and other serious AEs, >= Grade 3 AEs or AESIs
- AEs, regardless of tisagenlecleucel relationship, by primary SOC, PT and maximum grade
- AEs, regardless of tisagenlecleucel relationship, by PT and maximum grade
- AEs, suspected to be tisagenlecleucel related, by primary SOC, PT and maximum grade
- AEs, suspected to be tisagenlecleucel related, by PT and maximum grade
- Serious AEs (SAEs), regardless of tisagenlecleucel relationship, by primary SOC, PT and maximum grade
- Serious AEs (SAEs), regardless of tisagenlecleucel relationship, by PT and maximum grade
- Serious AEs (SAEs), suspected to be tisagenlecleucel related, by primary SOC, PT and maximum grade
- Serious AEs (SAEs), suspected to be tisagenlecleucel related, by PT and maximum grade
- Non-serious AEs, regardless of tisagenlecleucel relationship, by primary SOC and PT and maximum grade
- Non-serious AEs regardless of tisagenlecleucel relationship, by PT and maximum grade
- Non-serious AEs, suspected to be tisagenlecleucel related, by primary SOC and PT and maximum grade
- Non-serious AEs, suspected to be tisagenlecleucel related, by PT and maximum grade
- Non-serious AEs (threshold = 5%), regardless of tisagenlecleucel relationship, by primary SOC, PT and maximum grade

In addition, the following AE topics will be summarized:

- All AEs that started or worsened within 2 days of the leukapheresis procedure will be summarized for all subjects who received leukapheresis.
- All AEs that started or worsened during pre-lymphodepleting period will be summarized for enrolled subjects.
- All AEs, regardless of relationship to LD chemo, that started or worsened during lymphodepleting period will be summarized for subjects who received lymphodepleting chemotherapy.
- All AEs, suspected to be related to LD chemo, that started or worsened during lymphodepleting period will be summarized subjects who received lymphodepleting chemotherapy respectively.

All AE data (including those from the pre- lymphodepleting and lymphodepleting period) will be listed. In those listings the period will be displayed to enable a unique assignment of each AE to its corresponding reporting period.

2.8.2.1 Adverse events of special interest

Adverse events of special interest (AESIs) include all important identified and potential risks of tisagenlecleucel as per effective EU Risk Management Plan (RMP), and may also include additional relevant safety topics (e.g. missing information [redacted]). The list of AESIs and their search criteria are updated on a regular basis at program level in the electronic Case Retrieval Strategy (eCRS) form. The most recent version of the eCRS form will be used for the reporting activity.

For the safety post tisagenlecleucel infusion, AESIs will be summarized by drug relationship, group term, PT, maximum grade, and timing of onset: Within 8 weeks post tisagenlecleucel infusion, 8 weeks to 1 year post tisagenlecleucel infusion, >1 year post tisagenlecleucel infusion, and any time post tisagenlecleucel infusion.

AESI based on important identified risks and potential risks will be summarized for the post-infusion period by timing of onset:

- AESI post tisagenlecleucel infusion based on important identified risks, regardless of study drug relationship, by group term, PT and maximum grade
- AESI post tisagenlecleucel infusion based on important identified risks, suspected to be tisagenlecleucel related, by group term, PT and maximum grade
- Serious AESI post tisagenlecleucel infusion based on important identified risks, regardless of study drug relationship, by group term, PT and maximum grade
- Serious AESI post tisagenlecleucel infusion based on important identified risks, suspected to be tisagenlecleucel related, by group term, PT and maximum grade
- AESI post tisagenlecleucel infusion based on important potential risks, regardless of study drug relationship, by group term, PT and maximum grade
- AESI post tisagenlecleucel infusion based on important potential risks, suspected to be tisagenlecleucel related, by group term, PT and maximum grade
- Serious AESI post tisagenlecleucel infusion based on important potential risks, regardless of study drug relationship, by group term, PT and maximum grade

- Serious AESI post tisagenlecleucel infusion based on important potential risks, suspected to be tisagenlecleucel related, by group term, PT and maximum grade

All AESIs post tisagenlecleucel infusion based on identified and potential risks will be provided in a listing.

2.8.2.1.1 Cytokine release syndrome

Detailed information regarding the CRS episode of maximum grade, including duration of CRS, concurrent infections, timing and duration of high fever, timing and duration of intensive care unit (ICU) stay, selected complications and use of anti-cytokine therapies, etc. will be summarized by best overall response (CR/PR, MR/NR/PD and Unknown) and histology (BL and LBCL). In addition the maximum CRS grade per subject, the time to onset of CRS and the time to ≥Grade 3 CRS will be displayed.

Time to first CRS onset will be summarized for all subjects using the KM method. For those subjects without CRS, time to first onset will be censored. The censoring date is the minimum of the cut-off date, EOS evaluation and date of death (if applicable). Time to resolution of the first CRS will be summarized using KM method for subjects with CRS. In case the end date of a CRS is missing, it will be censored as the minimum of the cut-off date, EOS evaluation date and death date (if applicable).

CRS data will be listed according to the categories presented on the eCRF. Missing values are displayed if they are presented as such in the database.

2.8.2.1.2 Neurological events

Neurological events refer to a group of neurological AEs defined in the AESI search criteria form. A neurological event episode may include multiple overlapped or consecutive neurological AEs as long as the end date and the start date of two consecutive AEs are no more than 3 days apart (i.e., current AE Start date – previous AE End date ≤ 3). The onset day of a neurological event episode is the start date of the first neurological AE in the episode. The resolution date is the end day of the last AE in the episode. If there are multiple AEs with the same last end date and one or more of these AEs are unresolved, the entire episode will be considered unresolved.

Time to onset of the first neurological event episode will be summarized descriptively. Time to resolution of all neurological event episodes from all subjects will be summarized using KM method by ignoring the fact that multiple episodes might be clustered by subject. Meaning if we have one subject with 2 episodes, which are both included in the KM analysis, then the episodes are treated as if they are from 2 subjects (each with one episode) even though they are not completely independent. Time to resolution will be calculated by using the onset day of the neurological event episode as start date and the resolution date as end date. In case a neurological event does not resolve the last contact date is used as censoring date.

Neurological event episode post tisagenlecleucel infusion will also be summarized by their chronological relationship to CRS (i.e., before, during or after CRS). All neurological events and their onset time relative to CRS episodes will be listed.

2.8.3 Deaths

For the **safety post-tisagenlecleucel infusion**, summary tables by primary SOC and PT will be provided for all deaths that occurred after tisagenlecleucel infusion by timing of death: Within 30 days of tisagenlecleucel infusion, >30 days after tisagenlecleucel infusion and any time post tisagenlecleucel infusion.

All deaths will be listed. The reporting period as defined in Table 2-2 will be displayed in the listings.

2.8.4 Laboratory abnormalities

On analyzing laboratory, data from all sources (central and local laboratories) will be combined.

For laboratory tests covered by the CTCAE, the laboratory data will be graded according to CTCAE version 5.0, see Table 7-3. For these tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

Only parameters with non-missing standard results and units will be included in the analysis.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Shift tables using CTCAE grades to compare baseline to the worst post-infusion or safety comparison period value.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst post-infusion or safety comparison period value.
- Tables for laboratory abnormalities using CTCAE grades to compare post-baseline grade with baseline grade 0 to grade 2 worsened to post-baseline grade 3 to grade 4.

For the **safety post-tisagenlecleucel infusion**, the shift tables using CTCAE grades and normal ranges will be generated by timing: Within 8 weeks post tisagenlecleucel infusion, >8 weeks to 1 year post tisagenlecleucel infusion, >1 year post tisagenlecleucel infusion, and any time post tisagenlecleucel infusion.

Hematopoietic cytopenia is a reduction in the number of mature blood cells. It is commonly reported within 8 weeks of tisagenlecleucel infusion with grade 3/4 events. The percentage of subjects with grade 3 or above hematopoietic cytopenias 35 days post tisagenlecleucel infusion will be summarized.
Among subjects with Grade 3 or 4 hematopoietic cytopenias by 35 days post tisagenlecleucel infusion, time from tisagenlecleucel infusion to resolution of hematopoietic cytopenias to Grade 2 or below will be summarized using the KM method.

Grading of cytopenias will be derived using lab results in absolute lymphocytes (hypo), absolute neutrophils (hypo), hemoglobin (hypo), platelet count (hypo) or white blood cell (WBC) (hypo) according to CTCAE 5.0. If a subject did not achieve resolution at the last lab assessment, timing of resolution will be censored at the last assessment (latest available lab assessment based of all absolute lymphocytes, absolute neutrophils, hemoglobin, platelet count and white

blood cell assessments). The median time to resolution and KM estimates of % resolved cases at different time points (Month 3, Month 6 and etc.) will be summarized.

The following listings will be produced for the laboratory data:

- Listing of all laboratory abnormalities of CTCAE grade 3 or 4 with the corresponding CTCAE grades and the classifications relative to the laboratory reference ranges.

2.8.5 Percentage of subjects who undergo HSCT after tisagenlecleucel therapy

The percentage of subjects who undergo HSCT after tisagenlecleucel infusion among all subjects in the safety set will be summarized along with exact 95% CI into the following subgroups.

- While in remission
- With unknown remission status
- After relapse

2.8.6 Cytokine release syndrome

Clinical and biomarker data from this and other tisagenlecleucel studies will be analyzed to potentially identify an early predictive model which reflects the risk of developing severe cytokine release syndrome.

The goal of this statistical analysis should be considered as the generation of new scientific hypotheses and observing new trends, since the studies are not adequately powered to propose a scoring system.

Clinical and biomarker data will be analyzed to potentially identify an early predictive score which reflects the risk of developing severe cytokine release syndrome. Only parameters that can be potentially utilized in clinical setting by treating physicians will be considered for the score development.

This analysis will be peformed at the time of primary analysis and will not be repeated for the final analysis.

2.8.7 Growth data

Height and weight data will be listed by subject, and visit/time and if ranges are available, abnormalities will be flagged.

2.8.8 Tanner Staging

All Tanner staging data will be listed.

2.8.9 Other safety data

Presence of detectable RCL will be tested at protocol scheduled assessments and listed.

Vital signs will be collected as clinically needed and listed. Other relevant safety data will be listed.

2.9 Pharmacokinetic endpoints

Tisagenlecleucel concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed and summarized by time points as assessed by the following:

- CAR transgene levels as measured by qPCR
- CAR-positive viable T cells measured by flow cytometry of CD3-positive

[redacted]

The cellular kinetic parameters listed in Table 2-3 along with other relevant cellular kinetic parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix® (Pharsight, Mountain View, CA) and reported by best overall response category. The non-quantifiable concentrations with reported results will be imputed to zero for cellular kinetic concentration summaries. Results reported but deemed unreliable will be flagged and excluded from the summaries and cellular kinetic parameter derivations.

Table 2-2 Non-compartmental pharmacokinetic parameters

Parameter	Definition
AUC 0-28d and/or AUC 0-84d	The area under the curve (AUC) from time zero to day 28 and/or day 84 and or other disease assessment days, in peripheral blood (%×*days or days×*copies/µg)
Cmax	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (% or copies/µg)
Tmax	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
Clast	The last observed quantifiable concentration in peripheral blood (% or copies/µg)
Tlast	The time of last observed quantifiable concentration in peripheral blood (days)

[redacted]

2.9.1 Immunogenicity

The humoral immunogenicity assay measures the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. Data will be further fractionated to determine

proportion of subjects who make transient versus sustained antibody responses. The cellular immunogenicity assay assesses the presence of T lymphocytes activated by the tisagenlecleucel protein. Data will be reported as summary statistics of pre and post-dose levels of activated T lymphocytes.

2.9.1.1 Humoral immunogenicity

Humoral immunogenicity levels and the proportion of humoral immunogenicity positive and negative subjects will be summarized by time point. A strip plot of anti-tisagenlecleucel antibodies by time point will be presented. Regarding the boosted/induced humoral immunogenicity, a subject is only defined as positive for tisagenlecleucel treatment-induced or -boosted anti-mouse CAR19 (antimCAR19) antibodies when the anti-mCAR19 antibody MFI at any time post-infusion was at least 2.28-fold higher than pre-infusion levels. A summary of cellular kinetic parameters will be presented by categories of subjects with and without treated induced boosted/induced anti-tisagenlecleucel antibodies.

A scatter plot of baseline anti-tisagelecleucel antibodies versus qPCR AUC0-28d and Cmax will be presented along with the appropriate regression line. In addition, a boxplot of anti-tisagelecleucel antibodies at baseline by best overall response will be presented. The same disease response categories will be used for a similar boxplot summarizing the maximum fold-change (based on post-infusion/baseline MFI at various time points) of anti-tisagenlecleucel antibodies post-infusion.

2.9.1.2 Cellular immunogenicity

All analyses described in this section will be performed separately for both CD4 and CD8 T cell responses related to Pool 1 and Pool 2 peptides. The cellular immunogenicity will be summarized by best overall response. Strip plots will be presented with time points on the x-axis and net responses on y-axis. Additionally, a strip plot of maximum net response of cellular immunogenicity by best overall response will be displayed. A scatter plot of maximum net response post baseline versus qPCR AUC0-28d and Cmax will also be presented along with the appropriate regression line.

2.10 Additional analyses to assess the impact of COVID-19 pandemic

The impact of the COVID-19 pandemic on study population, efficacy and safety endpoints will be assessed by performing additional subgroup and supportive analyses. These analyses are in accordance with the Novartis COVID-19 guidance on impact on integrity and interpretability of clinical trials and with the Novartis COVID-19 guidance for developing clinical study reports for studies conducted during the COVID-19 pandemic.

The number and percentage of subjects enrolled, infused with tisagenlecleucel and discontinued during the pre-COVID-19 pandemic period, the COVID-19 pandemic period and the post-COVID-19 pandemic period (if applicable) will be summarized by region and country on the enrolled set. The corresponding pandemic periods are defined based on the start and end date of the pandemic in the respective region/country (see Novartis COVID-19 guidance for start and end dates by region for sensitivity analyses).

A subject will be assigned to the pre-pandemic, pandemic or post-pandemic period depending on his/her tisagenlecleucel infusion date.

Demographics, baseline disease characteristics and primary disease history will be summarized by pandemic period on the FAS to assess the impact of the COVID-19 pandemic on the study population.

Number and percentage of subjects with COVID-19 related protocol deviations will be summarized separately by deviation term and relationship to the COVID-19 pandemic on the FAS. In addition all PDs related to COVID-19 will be listed for the Enrolled Set.

To assess the impact of COVID-19 on safety and to assess possible regional differences in reporting of AEs, the 10 most frequent AEs (over all regions and pandemic periods) will be summarized by PT, region and pandemic set.

Additionally AEs and concomitant medications will be separately listed for subjects infected with COVID-19.

2.11 Biomarkers

As a project standard, Novartis Oncology Biostatistics will analyze only biomarkers collected in the clinical database. [redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood due to either practical or strategic reasons (e.g. issues related to the quality of the samples). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

The analyses to be performed for the CSR are outlined below. Additional analyses that may be performed after the completion of the EOS CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum to this document or as a stand-alone analysis plan document, as appropriate.

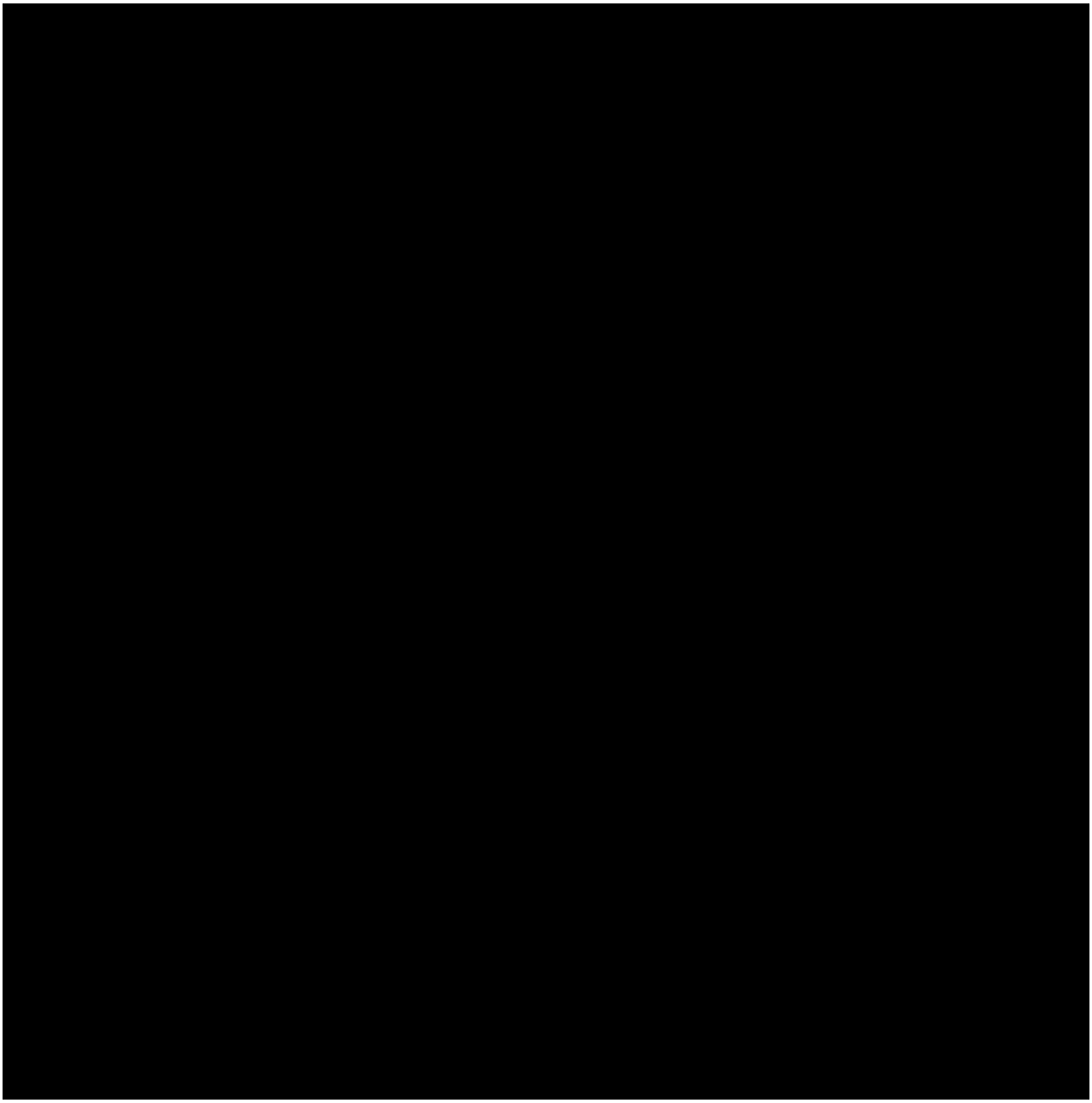
2.11.1 Biomarker Data Analysis Set

The FAS will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on subjects with biomarker data. Assessment of associations between biomarker and safety data will be conducted using the safety set.

2.11.1.1 Data Handling of Serum Cytokine Data

Serum cytokine data represent quantitative soluble protein measurements. Values below the lower limit of quantitation (LLOQ) (which may be reported with the label "LLOQ" or have a numerical value below the assay's LLOQ) will be imputed / replaced as 0.5×LLOQ, which will be specified by the performing lab and is assay and analyte specific. In some cases a value, although below LLOQ, is reported, this value should not be used and the data should be imputed as 0.5×LLOQ.

For values above the upper limit of quantification (ULOQ) (either reported as "ULOQ" or a numerical value greater than the assays upper limit of quantification), the values will be set to the ULOQ threshold of the assay.



[redacted]

3 DMC and interim analysis

To monitor safety and efficacy data obtained in the study, several interim analyses will be conducted to ensure the subjects' safety, the efficacy of the study drug and the compliance of the trial data with scientific and ethical standards.

3.1 Safety Data Monitoring Committee (DMC) analysis

Specific details regarding composition, responsibilities, data monitoring and meeting frequencyas well as documentation of DMC reports, minutes and recommendations will be described in the DMC charter.
According to the DMC charter the initial meeting of the DMC will be held mid-study approximately 14 months post the first subject enrollment. It will be an Open Meeting to establish rules and give the DMC an understanding of the trial expectations of Novartis and the Steering Committee. Subsequent safety reviews will occur approximately every 6 months, unless otherwise requested by the DMC. These meetings will have Open and Closed Sessions.

Based on the review of the open and closed DMC reports or equivalent safety reports, if appropriate, the DMC can recommend on continue the trial as planned without change, continue the trial but with recommended modification and interrupt or stop further treatment or place trial recruitment on hold because of safety concerns.

The reports for each interim safety meeting will summarize:

- Subject disposition, demographics and baseline characteristics
- Disease history
- Protocol deviations
- Prior and post tisagenlecleucel infusion medications and therapies, including information regarding prior/concomitant medications, prior/post antineoplastic medications, prior/post radiotherapies, prior/post surgeries, LD/bridging chemotherapies and prior/post hematopoietic stem cell transplants
- Tisagenlecleucel exposure
- Key laboratory abnormalities
- Deaths and adverse events, including serious adverse events, Grade 3/4/5 adverse events, adverse events leading to study withdrawal, adverse events of special interest and adverse events based on potential/identified risk
- Index/Non-Index/New lesion measurements, PET-review and bone marrow biobsy/aspirate and CRF assessments

Additionally certain efficacy reports, i.e. best overall response (BOR) and overall response rate (ORR), will be provided.

Of note, the above list is not exhaustive, upon DMC members' request other data may be provided (e.g. overall disease response).

The shells which will be used for the DMC analysis will be based on the shells planned for the CSR. A separate document including all corresponding shells will be prepared.

3.2 Primary and final analysis

It is planned to enroll approximately 35 subjects with an aim to infuse at least 26 evaluable subjects with aggressive r/r B-cell NHL (BL, DLBCL, PMBCL and GZL) for the primary ORR analysis.

The primary efficacy analysis will be based on all evaluable subjects with aggressive r/r B-cell NHL. The safety analysis will include all subjects who were enrolled in the study. The primary efficacy and safety analyses will be conducted when all evaluable subjects with aggressive r/r B-cell NHL have been infused and followed for at least 6 months from study day 1 or discontinued early as well as at least 50% of those subjects have a follow-up of at least 9 months.

A final Clinical Study Report (CSR) will be produced once all subjects complete the study, i.e. 2 years after LPLV.

4 Sample size calculation

The primary objective of the study is to estimate response rate and therefore the sample size is not based on power calculation. Among 26 subjects with aggressive r/r B-cell NHL, ORR will be descriptively summarized with the point estimate along with 95% exact CIs. With a sample size of 26 subjects, the 95% exact CI assuming various observed response rates are displayed in Table 4-1.

Table 4-1 95% exact CI assuming various observed response rates

Observed response rate (%)	95% exact CI (%)
38 (10/26)	20.2, 59.4
50 (13/26)	29.9, 70.1
62 (16/26)	40.6, 79.8

In addition, it is planned to ensure that there are at least 18 infused pediatric subjects with aggressive r/r B-cell NHL for the subgroup analysis of subjects <18 years. There is no pre-specified target for the number of FL subjects to be treated because it is an extremely rare and indolent disease. However enrollment in this subtype will be open until at least 26 subjects, including at least 18 pediatric subjects, with the aggressive subtypes for primary analysis have been treated.

5 Change to protocol specified analyses

No changes from protocol specified analyses have been made.

6 References

1. Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-722.
2. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
3. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
4. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
5. Sandlund JT, Guillerman RP, Perkins SL, et al (2015) International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncology; 33(18):2106-11.

7 Appendix

7.1 Imputation rules

7.1.1 Study drug

Missing dates for study drug administraton should be queried and will not be imputed.

7.1.2 AE, ConMeds and safety assessment date imputation

Table 7-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 7-2 Imputation of end dates (AE)

Missing Element	Rule
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by min(cut-off date, EOS evaluation, date of death, WOC date)
day, month	• If partial end date contains year only, set end date = min(31DEC, cut-off date, EOS evaluation, date of death, WOC date)
day	• If partial end date contains month and year, set end date = min(last day of the month, cut-off date, EOS evaluation, date of death, WOC date)

Partial or missing ConMeds end dates will not be imputed.

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

7.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer, first relapse and date of most recent recurrence/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: July 1st of the year

Incomplete assessment dates for tumor assessment

All investigation dates (e.g., MRI scan, computerized tomography (CT) scan, peripheral blood, bone marrow) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these 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. MRI scan, CT scan, peripheral blood, bone marrow) if the overall response at that assessment is CR/PR/NR/MR/PD/NOT EVALUABLE/UNK. Otherwise – if overall response is progression or 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 progression/relapse/no response. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

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.

Date of hospitalization imputation

Missing hospitalization end date or end date after data cut-off will be imputed following the same conventions as for AE end date imputation.

Incomplete date for death or last known date subject alive

If the day or month of death is missing from the death CRF, death will be imputed to the maximum of the full (non-imputed) last contact date (Section 2.1.1) and the following:

- Missing day: 15th day of the month and year of death
- Missing day and month: July 1st of the year of death

If the day or month of last known date subject alive is missing in the survival CRF, 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 July 1st 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 as defined in Section 2.1.1.

7.2 Laboratory parameters derivations

For laboratory tests covered by CTCAE, the laboratory data is graded according to Table 7-3.

Table 7-3 CTC grades for laboratory values based on CTCAE v5

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v5 – Nov 2017)

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				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9 /L	< 3.0 – 2.0 x 10^9 /L	< 2.0 – 1.0 x 10^9 /L	< 1.0 x 10^9 /L
WBC (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9 /L	-
Hemoglobin (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M) *(16.113 x mmol/L = g/L)*	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB			Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils ↓	10^9/L	NEUT		≥2x10^9 /L	< 2.0 - 1.5 x 10^9 /L	< 1.5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L
Lymphocytes↓	10^9/L	LYM		≥1.5x10^9 /L	< 1.5 - 0.8 x 10^9 /L	< 0.8 - 0.5 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L	< 0.2 x 10^9 /L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9 /L	> 20 x 10^9 /L	-
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine ↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol**/L or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	Defined by clinical criteria only in CTCAE V5				

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v5 – Nov 2017)

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				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	Defined by clinical criteria only in CTCAE V5				
Calcium (corrected) (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	Defined by clinical criteria only in CTCAE V5				
Glucose (fasting) (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*					
Glucose (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	< 129 - 125 mmol/L	< 124 - 120 mmol/L	< 120 mmol/L
Triglyceride ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR↑	1	INR	**0.8 – 1.2**	≤ 1.2	> 1.2- 1.5	> 1.5- 2.5	> 2.5	-
Activated partial thromboplastin time↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen ↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≥ ULN.
Clinical criteria such as 'asymptomatic' or 'Life-threatening consequences' are not considered for determination of LAB CTC grades. Concomitant usage of therapy is also not considered.
Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ 1.5 x 109 /L (lymphocytes) and ≥ 2 x 109 /L (neutrophils) are considered as LAB CTC grade 0
The **comparison with baseline is not considered** for derivation of LAB CTC grades

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

7.3 Study drug dose derivation

The cell count infused are calculated by multiplying the appropriate cell count with the 'Actual Percent Volume Infused'/100. The total over all bags is calculated by subject and visit. The weight for manufacturing, which is used for the assignment of each subject either to the ≤50 kg or the >50 kg group, is calculated by dividing 'Total infused CAR-positive viable T cells count (10^8)' by 'Total infused CAR-positive viable T cells count per kg (10^6/kg)' and multiplying with 100. If one of the cell counts is missing the last non-missing weight prior to infusion from vital signs is used as weight for manufacturing.

7.4 Statistical models

7.4.1 Primary analysis

Analysis of time to events Data

Kaplan-Meier estimates

For time-to-event analyses (DOR, RFS, EFS and OS), the survival 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% CI calculated from PROC LIFETEST output using the loglog option available within PROC LIFETEST, KM estimates with 95% CI 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 DOR). 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.

In completing risk analysis, the cumulative incidence function (CIF) can be estimated following macro:

```
%CIF(data=dataset, out=est, time=survtime, status=status, event=1);

/* survtime represents variable containing event/censor times;

status represents status variable (0=censored, 1= event of interest, 2= competing
events); */
```

An estimate of the survival function will be constructed using KM (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival will be obtained along with 95% CI calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. KM estimates of the survival function with 95% CI at specific time points will be summarized. The standard error of the KM estimate will be calculated using Greenwood's formula [Collett 1994].

Analysis of Binary Data

Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial CI (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper and Pearson 1934]

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) and two-sided Pearson-Clopper CI.

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

```
PROC FREQ data=dataset;

EXACT BINOMIAL;

TABLE outcome/binomial(p=0.2) ALPHA=0.xxx;

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.*/
```

7.5 Time windows

In order to summarize the PK, immunogenicity, biomarker, growth and Tanner staging 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 cutoffs 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 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. For PK, immunogenicity and biomarker data the mean value will be calculated in case two or more assessments are equidistant from the planned date. If two or more efficacy assessments have the same distance from the planned date the first assessment will be used.

Table 7-4 Time windows for biomarker data

Time Window (Protocol)	Planned visit timing (Study day)	Time Window Definition (Study days)
Cytokines (serum)		
W-12 to W-1 Enrollment	Before Study Day -7	< First day of LD chemotherapy
D-1 Pre-infusion	-1	First day of LD chemo to last day prior to infusion
D2	2	1 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 15
D17±3d	17	16 to 19
D21±3d	21	20 to 24
D28±7d	28	≥ 25
[redacted]		
Immunogenicity, Humoral (serum)		
W-12 to W-1 Enrollment	Before Study Day -7	< First day of LD chemotherapy

D-14 to D-2 Lymphodepleting chemotherapy	-2	First day of LD chemo to last day prior to infusion
D14±3d	14	1 to 21
D28±7d	28	22 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 274
M12±14d	365	275 to 456
M18±28d	548	457 to 639
M24±28d	731	≥ 640
Immunogenicity, Cellular (peripheral blood)		
W-12 to D-1 +1d Enrollment/Pre-infusion	-1	≤ Last day prior to infusion
D28±7d	28	1 to 59
M3±14d	91	60 to 137
M6±14d	183	138 to 274
M12±14d	365	275 to 456
M18±28d	548	457 to 639
M24±28d	731	≥ 640

[redacted]

Table 7-5 Time windows for PK data

Time Window (Protocol)	Planned visit timing (Study day)	Time Window Definition (Study days)
Tisagenlecleucel cellular kinetics by qPCR (peripheral blood) and tumor clonal typing by deep sequencing analysis (peripheral blood)		
W-12 to W-1 Enrollment	Before Study Day -7	≤ Last day prior to infusion
D4±1d	4	1 to 5
D7±1d	7	6 to 9
D11±1d	11	10 to 12
D14±3d	14	13 to 17
D21±3d	21	18 to 24
D28±7d	28	25 to 59
M3±14d	91	60 to 137
M6±14d	183	138 to 228
M9±14d	274	229 to 319
M12±28d	365	320 to 456
M18±28d	548	457 to 639

M24±28d	731	640 to 913
M36±28d	1096	914 to 1278
M48±28d	1461	1279 to 1643
M60±28d *	1826	≥ 1644
Tisagenlecleucel cellular kinetics by flow cytometry (peripheral blood)		
W-12 to D-1 +1 Enrollment/Pre-infusion	-1	≤ Last day prior to infusion
D7±1d	7	1 to 9
D11±1d	11	10 to 12
D14±3d	14	13 to 15
D17±3d	17	16 to 22
D28±7d	28	23 to 59
M3±14d	91	60 to 137
M6±14d	183	138 to 228
M9±14d	274	229 to 319
M12±28d	365	320 to 456
M18±28d	548	≥ 457
Tisagenlecleucel cellular kinetics by qPCR (bone marrow)		
W-12 to D-1 +1 Enrollment/Pre-infusion	-1	≤ Last day prior to infusion
M3±14d	91	1 to 137
M6±14d**	183	138 to 228
M9±14d**	274	229 to 319
M12±28d**	365	320 to 456
M18±28d**	548	457 to 639
M24±28d**	731	≥ 640
Tisagenlecleucel cellular kinetics by flow cytometry (bone marrow) and tisagenlecleucel cellular kinetics by qPCR in CSF		
D -1 Pre-infusion**	-1	≤ Last day prior to infusion
D28±7d**	28	1 to 59
M3±14d**	91	60 to 137
M6±14d**	183	138 to 228
M9±14d**	274	229 to 319
M12±28d**	365	320 to 456
M18±28d**	548	457 to 639
M24±28d**	731	≥ 640
RCL by VSV-G qPCR (peripheral blood)		
W-12 to W-1 Enrollment	Before Study Day -7	≤ Last day prior to infusion
M3±14d	91	1 to 137
M6±14d	183	138 to 274
M12±28d	365	275 to 548
M24±28d	731	549 to 913
M36±28d	1096	914 to 1278
M48±28d	1461	1279 to 1643
M60±28d *	1826	≥ 1644

Study Day 1 = Start date of tisagenlecleucel

*Measures continue annual while still in follow-up meaning there could potentially also be visits at M72, M84, etc. Additional time windows should be included as necessary.

**At relapse or as clinically indicated.

[redacted]

Table 7-7 Time windows for growth data and Tanner staging

Time Window (Protocol)	Planned visit timing (Study day)	Time Window Definition (Study day)
Height		
W-16 to W-1 Screening	Before Study Day -7	< Last day prior to infusion
D-1+1d Pre-infusion	-1	Last day prior to infusion to Day 1 pre-infusion
D28±7d	28	1 to 59
M3±14d	91	60 to 137
M6±14d	183	138 to 228
M9±14d	274	229 to 319
M12±28d	365	320 to 456
M18±28d	548	457 to 639
M24±28d	731	640 to 913
M36±28d	1096	914 to 1278
M48±28d	1461	1279 to 1643
M60±28d *	1826	≥ 1644
Weight		
W-16 to W-1 Screening	Before Study Day -7	< First day of LD chemotherapy
D-14 to D-2 Lymphodepleting chemotherapy	-2	First day of LD chemo to Day -2
D-1+1d Pre-infusion	-1	Day -1 to Day 1 pre-infusion
D2	2	1 to 4
D7±1d	7	5 to 10
D14±3d	14	11 to 17
D21±3d	21	18 to 24
D28±7d	28	25 to 59

M3±14d	91	60 to 137
M6±14d	183	138 to 228
M9±14d	274	229 to 319
M12±28d	365	320 to 456
M18±28d	548	457 to 639
M24±28d	731	640 to 913
M36±14d	1096	914 to 1278
M48±14d	1461	1279 to 1643
M60±14d *	1826	≥ 1644
Tanner Staging		
W-16 to W-1 Screening	Before Study Day -7	≤ Last day prior to infusion
M6±14d	183	1 to 274
M12±28d	365	275 to 548
M24±28d	731	549 to 913
M36±28d	1096	914 to 1278
M48±28d	1461	1279 to 1643
M60±28d*	1826	≥ 1644
Chemistry laboratory assessments (e.g. Ferritin, CRP)		
W-16 to W-1 Screening	Before Study Day -7	< First day of LD chemotherapy
D-14 to D-2 Lymphodepleting chemotherapy	-2	First day of LD chemo to last day prior to infusion
D1	1	1
D2	2	2
D4±1d	4	3 to 5
D7±1d	7	6 to 9
D11±1d	11	10 to 12
D14±3d	14	13 to 15
D17±3d	17	16 to 19
D21±3d	21	20 to 24
D28±7d	28	25 to 59
M3±14d	91	60 to 137
M6±14d	183	138 to 228
M9±14d	274	229 to 319
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M18±28d	548	457 to 639
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M60±28d*	1826	≥ 1644

Study Day 1 = Start date of tisagenlecleucel

*Measures continue annual while still in follow-up meaning there could potentially also be visits at M72, M84, etc. Additional time windows should be included as necessary.