NOVARTIS

Clinical Development

CTL019/ Tisagenlecleucel/KYMRIAH

CCTL019E2202 / NCT03568461

A Phase II, single arm, multicenter open label trial to determine the efficacy and safety of tisagenlecleucel (CTL019) in adult patients with refractory or relapsed follicular lymphoma

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final

Release date: 7-May-2021

Number of pages: 39

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
26-Nov-2018	Prior to FPFT	Creation of final version	N/A - First version	NA
13-July-2020	Prior interim analysis	Creation of amendment 1	Defintion of the interim efficacy analysis and clarifications on the analysis sets: Section 2.2 Update and clarifications on subgroup of interest for efficacy analysis: Section 2.2.1 Clarifications on endpoints for diagnosis and extend of cancer: Section 2.3.5 Addition of a listing for protocol deviations due to COVID: Section 2.3.6 Addition of prior anti-neoplastic refractory and IVIg data analyis: Section 2.4.2 Clarification of the primary endpoint analysis at interim analysis: Section 2.5.2 Removal of the censoring rule "Event documented after at least two missing tumor assessments" for DOR and PFS analysis: Sections 2.7.2 and 2.7.3 Addition of few safety analysis and clarifications provided to align with project level standard: Section 2.8 [redacted] Overall: • Clarification on the analysis perfomred at the interim analysis and primary analysis • Other minor changes to improve the overall quality and align with standards.	
10-Nov-2020	Prior primary analysis	Creation of amendment 2	Addition of treatment density and bulky disease as prognostic variables: Sections 2.2.1 and 2.3.4 [redacted]	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Other minor changes added for clarification or to improve the overall quality and align with standards.	
21-Apr-2021	Prior extended Follow-up analysis	Creation of amendment 3	Update and clarifications on subgroup of interest for efficacy analysis: Section 2.2.1 Additional sensitivity analysis for primary endpoint: Section 2.5.4 Clarification on the competing risk analysis for DOR: Section 2.7.2. Addition of PFS and OS analysis based on time from enrollment: Sections 2.7.3 & 2.7.4 Update of the prolonged cytopenia and liver toxicity analysis to align with program level standard: Section 2.8.3. Update on immunogenicity analysis to align with protocol objectives/ endpoints: Section 2.8.4. Addition of analysis to assess the impact of COVID-19 pandemic: Section 2.13.	
7-May-2021	Prior extended Follow-up analysis	Creation of amendment 4	Addition of the modified efficacy analysis set for efficacy endpoints (upon FDA' request): Sections 2.2, 2.5 and 2.6. Clarification provided on the derivation for PFS/ OS from enrollment: Section 5.7.	

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomical therapeutic classification
AUC	Area under the curve
BOR	Best overall response
CAR	Chimeric antigen receptor
CI	Confidence interval
CK	Cellular kinetic
CKAS	Cellular Kinetic Analysis Set
CR	Complete response
CRO	Contract research organization
CRP	C-reactive protein
CRR	Complete response rate
CRS	Cytokine release syndrome
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DMC	Data Monitoring Committee
DOR	Duration of response
DRL	Drug reference listing
EAS	Efficacy analysis set
ECG	Electrocardiogram
EQ-5D-3L	Euopean quality of life - 3 dimensions
FAS	Full analysis set
eCRF	Electronic case report rorm
FACT-Lym	The functional assessment of cancer therapy - lymphoma
FL	Follicular lymphoma
FLIPI	Follicular lymphoma international prognostic index
[redacted]	[redacted]
IRC	Independent review committee
MedDRA	Medical dictionary for drug regulatory affairs
MRI	Magnetic resonance imaging
NCI	National cancer institute
LPLV	Last patient last visit
ORR	Overall response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase

PK	Pharmacokinetics
PPS	Per-protocol Set
PR	Partial response
PRO	Patient-reported outcomes
PT	Preferred term
QoL	Quality of life
r/r	Replased or refractory
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCT	Stem cell transplant
SD	Standard deviation
SF-36	Short form 36 health survey
SOC	System organ class
TFLs	Tables, figures, listings
[redacted]	[redacted]
WBC	White blood cells
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CCTL019E2202, a phase II, single arm, multicenter open label trial to determine the efficacy and safety of tisagenlecleucel (CTL019) in adult patients with refractory or relapsed follicular lymphoma (FL). The content of this SAP is based on protocol CCTL019E2202 v00, with slight changes in the definition of analysis sets, which will be specified as changes from protocol specified analyses in the CSR.

1.1 Study design

This single arm, multi-center, open label, phase II study to determine the efficacy and safety of tisagenlecleucel in adult patients with r/r FL, has the following sequential phases: Screening, Pre-treatment, Treatment, and Follow-up. Treatment and Follow-up will include infusion and safety and efficacy follow-up for at least 24 months. All patients who have received tisagenlecleucel, will additionally be followed up for survival follow-up every 3 months.

Efficacy will be evaluated using PET/CT/MRI based on Lugano classification (Cheson et al 2014) response criteria (see protocol Appendix 14.1). Imaging will be performed at Months 3, 6, 9, 12, 18, 24 months, and every 6 months thereafter (if applicable), and at any time disease progression or relapse is suspected, until disease progression or relapse, start of new anticancer therapies, death, lost to follow-up or withdrawal of consent.

The primary analysis will be performed when 90 patients have received tisagenlecleucel infusion and have completed 6 months from study day 1 infusion or discontinued earlier. In addition, one interim analysis is planned when approximately 50 patients have received tisagenlecleucel infusion and all of them have completed 6 months from infusion or discontinued earlier. The study will not be stopped for outstanding efficacy at the interim analysis regardless of the analysis results.

1.2 Study objectives and endpoints

The primary objective of this study is to evaluate the efficacy of tisagenlecleucel with respect to complete response rate. A list of study objectives and related endpoints are provided in Table 1-1 below.

Table 1-1 Study objectives and endpoints

Objective	Endpoint
Primary	
Evaluate the efficacy of tisagenlecleucel therapy as measured by CRR determined by IRC	Complete response rate (CRR) determined by an Independent Review Committee (IRC) in the efficacy analysis set (EAS) based on Lugano 2014 classification response criteria (Cheson et al 2014).
Key secondary	
Not applicable	Not applicable
Other Secondary	
	ORR, including complete response (CR) and partial response (PR) determined by IRC in the EAS based on Lugano 2014 classification.

Objective	Endpoint
Evaluate the efficacy of tisagenlecleucel as measured by additional efficacy measures, including ORR, DOR, PFS and OS	DOR, defined as time from achievement of CR or PR to progression or death due to FL, based on IRC DOR for CR only, defined as time from achievement of CR to relapse or death due to FL, based on IRC PFS, defined as time from tisagenlecleucel infusion to first documented disease progression or death due to any cause, based on IRC OS, defined as time from tisagenlecleucel infusion to death due to any cause
Evaluate safety of tisagenlecleucel	Type, frequency and severity of adverse events and laboratory abnormalities
Characterize the *in vivo* cellular kinetics (levels, expansion, persistence) of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, and other tissues if available) and CD3+ tisagenlecleucel cells in peripheral blood, summarized by clinical response	Summary of qPCR detected tisagenlecleucel transgene concentrations in peripheral blood, bone marrow and other tissues by time point and clinical response status Summary of cellular kinetic parameters: Cmax, Tmax, AUC0-28 and AUC0-84d, T1/2, and/or other relevant parameters in peripheral blood; bone marrow and other tissues by clinical response as appropriate Summary of exposure and cellular kinetic parameters of CD3+ tisagenlecleucel cells in peripheral blood detected by flow cytometry
Characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular)	Summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel
Characterize the impact of pre-existing and treatment induced immunogenicity (cellular and humoral) on cellular kinetics, efficacy and safety	Levels of pre-existing and treatment induced immunogenicity Cellular kinetic parameters (Cmax, AUCs, Tlast), concentration-time profile tisagenlecleucel by immunogenicity category (positive/negative) Efficacy (ORR, DOR, PFS) Safety (B-cell levels, CRS grades, neurologic events)
Describe the effect of tisagenlecleucel therapy on Patient reported outcomes (PRO)	Summary scores of PRO measured by SF-36 version 2, EQ-5D-3L and FACT-Lym quality of life questionnaires

Objective	Endpoint
[redacted]	

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The data cut-off date will be established:

- for the primary analysis after 90 patients have received tisagenlecleucel infusion and have completed 6 months from study day 1 infusion or have discontinued earlier;
- for the interim analysis after approximately 50 patients have received tisagenlecleucel infusion and have completed 6 months from infusion or discontinued earlier.

All statistical analyses will be performed using all data collected in the database up to the cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with a start date before or on the cut-off date and an end date after the cut-off date will be reported as ‘ongoing’. The same rule will apply to events starting before or on the cut-off date and not having documented an end date. This approach will apply to adverse events

and concomitant medications. For these events, the end date will not be imputed and therefore will not appear in the listings. Post primary analysis, a data cut-off will be established when 90 infused patients will have completed 12 months from study day 1 infusion or have discontinued earlier. Afterward, selected efficacy and safety analysis may be updated as needed.

The final CSR will be produced once all patients have completed the study.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients 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, if applicable. Percentages will be calculated using the number of patients 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, median, minimum, and maximum).

For PK concentration and PK parameters, coefficient of variation (CV) (%), geometric mean, and geometric CV% will be presented in addition to the previously mentioned summary statistics.

CV (%) will be calculated as: 100*(SD/arithmetic mean).

Geometric CV (%) will be calculated as: sqrt (exp (variance for log transformed data)-1)*100.

Unscheduled assessments

The following points summarize the rules for unscheduled assessments:

- Baseline: All unscheduled assessments before the treatment start should be considered when determining the baseline value.
- In summary tables by visit, unscheduled assessments should not be included unless they qualify as baseline.
- In shift and abnormality tables, all unscheduled assessments should be included.

Unscheduled assessments will be reported with the scheduled assessments in the listings.

2.1.1 General definitions

Study treatment

Study treatment refers to tisagenlecleucel.

Completion of treatment

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

Start date of treatment

The start date of the treatment is defined as the date of the administration of tisagenlecleucel.

End date of treatment

The end date of the treatment is defined as the date when tisagenlecleucel was administered.

Study day

The study day, describes the day of the event or assessment date, relative to the date of tisagenlecleucel infusion. Study day 1 for all assessments is the date of tisagenlecleucel infusion.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) – the date of tisagenlecleucel infusion + 1, if event is on or after the date of tisagenlecleucel infusion;
- The date of the event (visit date, onset date of an event, assessment date etc.) – the date of tisagenlecleucel infusion, if event precedes the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the start of study treatment, the study day displayed in the listing will be negative. In addition, days from the date of enrollment will be calculated and listed for selected analyses.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For baseline disease evaluations, the most current assessments (bone marrow, CSF, etc.) on or prior to the date of tisagenlecleucel infusion will be used as the baseline assessment.

For safety evaluations, the last available assessment on or before the date of tisagenlecleucel infusion is taken as ‘baseline’ assessment. In case time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline.

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

For safety parameters other than ECG, scheduled pre-dose collections as well as unscheduled collections on Day 1 for which no time is available will be considered as pre-dose.

For ECG, study Day 1 scheduled pre-dose ECGs will be considered to have been obtained prior to start of study treatment if dosing time or ECG time is missing and used in the calculation of the baseline value. If a scheduled pre-dose measurement actually occurred post-dose, then the

corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Duration of study follow-up

Duration of study follow-up is defined as the duration from the date of enrollment until analysis data cut-off for interim analyses or LPLV for final CSR.

Last contact date

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

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 from concomitant medications, PRO, 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. Partial dates imputation is only allowed for event (death) dates and censoring dates coming from Survival Follow-up eCRF page.

Lost to follow up

For overall survival 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 analysis (i.e. DOR and PFS), subjects will be considered as lost to follow-up if the subject has discontinued the study due to lost to follow-up.

2.2 Analysis sets

The analysis sets to be used are defined as below. The interim efficacy analysis set (IEAS) and efficacy analysis set (EAS) will be used as primary efficacy analysis set for the interim and

primary analysis repectively. The safety set will be used for all safety analyses. The cellular kinetic analysis set (CKAS) will be used for cellular kinetic analysis.

Screened Set

The screened set comprises all subjects who have signed informed consent and have been screened in the study.

Enrolled Set

The enrolled set comprises all subjects who have been enrolled in this study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients' leukapheresis product is received and accepted by the manufacturing facility.

Tisagenlecleucel Infused Set

The tisagenlecleucel infused set comprises all subjects who have received tisagenlecleucel.

Efficacy Analysis Set

The efficacy analysis set (EAS) includes all subjects who have received tisagenlecleucel and had measurable disease at baseline per IRC. Non-measurable disease at baseline is defined as absence of index lesion at baseline disease evaluation (i.e. no disease at baseline).

Modified Efficacy Analysis Set

The modified efficacy analysis set (mEAS) includes the first 90 subjects who have received tisagenlecleucel and had measurable disease at baseline per IRC.

Interim Efficacy Analysis Set

At the time of interim analysis, the Interim Efficacy Analysis Set (IEAS) comprises all subjects who have received tisagenlecleucel infusion at least 166 days (i.e. 6 months considering 14 days time-window) prior to the data cut-off date, had measurable disease at baseline per IRC and have either completed Month 6 assessment visit or discontinued efficacy follow-up earlier.

Safety Set

The safety set comprises all subjects who have received tisagenlecleucel. In this study the safety set contains the same subjects as the tisagenlecleucel infused set.

Per-Protocol Set

The per-protocol set (PPS) consists of a subset of subjects in the IEAS or EAS (at time of the interim and primary analysis respectively).

Protocol deviations leading to exclusion from the PPS include:

- No diagnosis of FL at baseline
- Missing or incomplete documentation of disease
- Receiving a dose less than the recommended dose of 0.6×10^8 tisagenlecleucel transduced viable T cells (i.e. total CAR-positive viable T cell count)

Cellular Kinetic Analysis Set

The cellular kinetic analysis set (CKAS) consists of subjects in the IEAS or EAS (at time of the interim and primary analysis respectively) who provide an evaluable cellular kinetic profile (at least one cellular kinetic parameter). The CKAS will be used for summaries (tables and figures) of cellular kinetic data. The tisagenlecleucel infused set will be used for listings of cellular kinetic data. Note that subjects may be removed from the estimation of certain CK parameters on an individual basis depending on the number of available samples. These subjects will be identified at the time of the analyses.

[redacted]

2.2.1 Subgroup of interest

The following subgroup of interest will be used for the supporting efficacy analysis of the Complete response rate (CRR).

- Age: <65 years, ≥ 65 years
- Gender: Male, Female
- Race: Asian (i.e. Chinese, Indian, Japanese Korean or Vietnamese), Black or African American, White, Native Hawaiian or Other Pacific Islander or American Indian, Alaska Native
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Follicular Lymphoma International Prognostic Index (FLIPI) at study entry: low/intermediate, high (defined in Section 2.3.5)
- Histological grade: 1, 2, 3A
- Number of prior lines of anti-neoplastic therapy: ≤2 lines, 3 to 4 lines, >4 lines
- PI3K inhibitor use: naïve, pretreated
- Prior HSCT therapy: yes or no; In addition, subjects who relpased ≤12 months from HSCT and >12 months from HSCT will be displayed.
- Disease status to last line of prior anti-neoplastic therapy: refractory, relapsed (defined in Section 2.3.5)
- Progression of disease within 24 months (POD24) from initiation of first-line anti-CD20 mAb containing therapy: yes, no (defined in Section 2.3.5)
- Bulky disease at baseline (defined per IRC as imaging showing any nodal or extra nodal tumor mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm): yes or no
- Bridging therapy: yes or no
- Lactate dehydrogenase (LDH) at study entry: ≤ULN or >ULN
- R2 use (Lenalidomide + Rituximab, within same regimen): naïve, pretreated

- Us sites: yes, no
- Total Metabilic tumor volume (MTV) at baseline: Low tumor burden (tumor volume ≤510 cm3 or High tumor burden (tumor volume >510 cm3).
- Double refractory (defined as subjects who failed to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen): yes, no

The following subgroup of interest will be used for the supporting key safety summaries of adverse events regardless of relationship to study drug by system organ class (SOC) and perferred term (PT), and adverse events of special interest.

- Age: <65 years, ≥ 65 years
- Gender: Male, Female
- Race: Asian (i.e. Chinese, Indian, Japanese, Korean or Vietnamese), Black or African American, White, Native Hawaiian or Other Pacific Islander or American Indian, Alaska Native
- Ethnicity: Hispanic or Latino, Not hispanic or latino
- Bulky disease at baseline: yes or no

The objective of carrying out these subgroup analyses is to evaluate the efficacy benefits and identify safety problems that are limited to a subgroup of patients or that are more commonly observed in a subgroup of patients.

Summary tables will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered.

In addition, key summary tables and/or figures will be developed for Japan subgroup, defined as all patients who have been enrolled in the study from the investigational sites located in Japan (i.e., Country = Japan), to address the regulatory submission in Japan. No statistical hypothesis testing will be conducted for Japan subgroup. Summary tables and/or figures developed for Japan subgroup will be specified in the tables, figures, listings (TFLs) shells document.

2.3 Subject disposition, demographics and other baseline characteristics

Unless specified otherwise, the enrolled setwill be used for all baseline and demographic summaries and listings, where subjects will be presented by whether they have received tisagenlecleucel infusion or not. In addition, selected summary tables will be presented for the IEAS.

2.3.1 Subject disposition

Subject disposition will be summarized as follows:

- Screening disposition for the Screened Set
- Treatment disposition for the Enrolled Set
- Study disposition for the Enrolled 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 captured in the Disposition eCRF pages.

Study follow-up will be summarized numerically as well as by categories: <6 months, 6 months to <12 months, 12 months to <24 months, and >=24 months for the enrolled set.

All disposition data will be listed using the Screened Set.

2.3.2 Analysis sets

The number (%) of subjects in each analysis set (defined in Section 2.2) will be summarized (using enrolled set as denominator). In addition, listings of patients excluded from the analysis sets will be provided.Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized. The following grouping will be applied: Age: 18-< 65, 65-<85, ≥85 years.

2.3.3 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed. Ongoing and historical medical conditions will be flagged separately in the listing. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

2.3.4 Diagnosis and extent of cancer

The summary of diagnosis and extent of cancer (i.e. disease history) will include stage at initial diagnosis, stage at time of study entry, bone marrow involvement at study entry, histological grade, any extralymphatic sites involved by lymphoma at study entry, time (in months) from first line of therapy, initial diagnosis, most recent relapse or progression to enrollment , number of previous lines of therapies, the Follicular Lymphoma International Prognostic Index (FLIPI) risk category at study entry, presence of B-symptoms at study entry (at least one symptom category reported as present), primary refractory and status of progression of disease within 24 months (POD24).

The POD24 status is defined as subjects experiencing disease progression or relapse within 24 months from initiation of first-line anti-CD20 mAb containing therapy. POD24 group will also include primary refractory subjects to a frontline therapy.

The FLIPI includes 5 labelled prognostic factors; FLIPI score will be derived as sum of (where prognostic factor ='Yes'). The FLIPI score will be categorized as follows:

- Low risk: score between 0 to 1
- Intermediate risk: score of 2
- High risk: score of 3 or more

Subjects will be classified by their disease status to last line of prior anti-neoplastic therapy as follow:

- Refractory: defined as subjects who had a Progression disease (PD) or Stable disease (SD) as best reponse from last line of prior therapy, or PD within 6 months from completion of last line of prior therapy;
- Relapsed: defined as subjects who had a Complete response (CR) or Partial response (PR) as best response from last line of prior therapy (and relapsed/progressedprior to the study entry) and relapsed after 6 months;

Bulky disease defined per IRC as imaging showing any nodal or extra nodal tumor mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm.

Treatment density will be derived for each subject based on the following algorithm: Time from initial diagnosis to study entry (year)/ number of line of prior therapy.

Primary refractory is defined as a subjects who had a PD or SD as best reponse from first line of prior therapy.

2.3.5 Protocol deviations

The number (%) of subjects with any protocol deviation will be tabulated by deviation category. Reasons leading to exclusion from per-protocol sets will be tabulated. All protocol deviations will be listed including protocol deviations due to COVID-19.

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

2.4.1 Study treatment / compliance

The tisagenlecleucel infused set will be used for all summaries and listings of study treatment.

Tisagenlecleucel

The total viable cell count infused and total CAR-positive viable T cell count will be listed and summarized using descriptive statistics.

Patients will be categorized as below, within or above the protocol-specified dose range. Time to infusion since screening and enrollment will be summarized using descriptive statistics.

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

Lymphodepleting chemotherapy and bridging therapy

The lymphodepleting and bridging chemotherapies, received after enrollment but prior to infusion will be summarized and listed. Patients will be summarized by the types of lymphodepleting chemotherapies received.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy, prior hematopoietic stem cell transplant or prior anti-

neoplastic surgery will be summarized. Summaries will include time from best response of CR/PR to last line of anti-neoplactic therapy to relapse or progression (DOR from last line of anti-neoplastic therapy) and prior refractory therapies. For radiotherapy, time since the last radiotherapy, locations and setting of the last therapy will be summarized.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables. Prior anti-neoplastic medications will be summarized by ATC class, and preferred term.

The above analyses will be performed using the enrolled set.

Post treatment antineoplastic therapy

Anti-neoplastic medications post tisagenlecleucel infusion will be listed and summarized by ATC class, preferred term by means of frequency counts and percentages using the tisagenlecleucelinfused set. Post treament transplant and radiotherapy will be listed.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the treatment and follow-up period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications starting on or after the date of infusion and
2. Medications starting prior to the date of infusion and continuing after the date of infusion.

All concomitant therapies will be listed. Any therapies starting and ending prior to the start of study treatment will be flagged in the listing. The enrolled set will be used for all concomitant medication listings.

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

[redacted] The frequency of anti-cytokine medications will also be summarized by preferred term using the tisagenlecleucel infused set.

In addition, summary of Immunoglobulin replacement therapy (IVIg) post tisagenlecleucel infusion will be summarized by BOR including number and percentage of subjects who received therapies and reason for therapy discontinuation.

2.5 Analysis of the primary objective

The primary objective is to evaluate the efficacy of tisagenlecleucel reflected by the complete response rate (CRR) determined by an independent review committee (IRC).

2.5.1 Primary endpoint

The primary endpoint is the CRR as determined by IRC. The CRR is defined as the proportion of patients with a best overall response of CR recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever comes first.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed by testing the null hypothesis of CRR being less than or equal to 15% at one-sided cumulative 2.5% level of significance, i.e.

$$H0: p \leq 0.\ 15 \text{ vs. } Ha: p > 0.15$$

The primary efficacy endpoint, CRR, will be analyzed at the interim look and final look of a group sequential design.
The CRR will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets as implemented in East 6.3 (Lan and DeMets, 1983).
The study will be considered successful if the lower bound of the 2-sided exact confidence interval for CRR is greater than 15%, so that the null hypothesis that the CRR is less than or equal to 15% can be rejected. P-value from binominal exact test will be provided.

The primary efficacy endpoint, CRR will be analyzed based on the data observed in the IEAS and the EAS at interim and pimary analysis respectively. In addition, sensitivity analysis will be performed using the local investigator response assessments instead of the IRC assessment.

2.5.3 Handling of missing values/censoring/discontinuations

Patients in this study who are of unknown clinical response will be treated as non-responders. See also the Novartis guideline for efficacy evaluation in lymphoma studies (based on Lugano 2014 response criteria) (Protocol Section 14.2) for more details.

Other missing data are noted as missing on appropriate tables/listings.

2.5.4 Sensitivity analyses

The primary analysis will also be performed on the Enrolled Set, tisagenlecleucel infused set, and PPS using the same methodology as well as on the mEAS and EAS excluding subjects who achieved CR at the radiologic assessment at baseline per IRC.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

IRC assessment will be used in the main analysis of secondary endpoints that involve disease response. Unless otherwise specified, all analyses of the secondary efficacy endpoints will be

performed on the IEAS and the EAS at interim and pimary analysis respectively. In addition, selected analyses will be performed for the mEAS, tisagenlecleucel infused set, and/or for the Enrolled set.

2.7.1 Overall response rate (ORR)

ORR is defined as the proportion of patients with a best overall disease response of CR or PR. The Best overall response (BOR) is defined as the best response recorded until progressive disease or start of new anticancer therapy or the data cut-off date, whichever is earlier. The ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence Intervals.

2.7.2 Duration of response (DOR)

DOR applies only to patients whose best overall disease response was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to Follicular lymphoma (FL). If a patient has not had an event, duration of overall response is censored at the date of the last adequate assessment.

In case a patient does not have progression or death due to FL prior to data cutoff, DOR will be censored at the date of the last adequate assessment 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)
- Adequate assessments no longer available

In the main analysis of DOR, death due to reason other than FL will be considered as a competing risk event to other events of interest (progression or death due to FL). In this analysis, the median response duration (if appropriate) as well as proportion of patients without events following response (progression or death due to FL) at 3, 6, 9, 12 months, etc. will be presented with 95% confidence intervals using the cumulative incidence function (CIF). The distribution function of DOR will also be estimated usingthe Kaplan-Meier method where ther the competing risk event, i.e. death ue to reason other than FL will be censored at the date of the last assessment with response of CR or PR on or prior to the censoring event.

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

Duration of response will be summarized for patients with CR only as well as with CR or PR.

2.7.3 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 or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of the last adequate assessment.

In case a patient does not have progression or death prior to data cutoff, PFS will be censored at the date of the last adequate assessment 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 (incl. HSCT)
- Adequate assessments no longer available

PFS will be estimated using the Kaplan-Meier method and the median PFS as well as proportion of patients without event at 3, 6, 9, and 12 months will be presented along with 95% confidence interval.

The PFS will also be analyzed as time from enrollment to the date of event defined as the first documented progression or death due to any cause for Enrolled set (see Section 5.7).

2.7.4 Overall survival (OS)

Overall survival (OS) is the time from date of first tisagenlecleucel infusion to date of death due to any reason. If a death has not been observed by the date of analysis cutoff, OS will be censored at the date of last contact.

The distribution function of OS will be estimated using the Kaplan Meier (KM) method. The median OS and the proportion of patients alive at 3, 6, 12, 18, and 24 months with 95% confidence intervals will be presented.

The OS will also be analyzed as time from enrollment to the date of death due to any reason for Enrolled set (see Section 5.7).

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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.

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
Pre-lymphodepleting period	From day of subject's informed consent to the day before first lymphodepleting chemotherapy dose or the day before infusion of tisagenlecleucel if the lymphodepleting chemotherapy is not given	Screened subjects
Lymphodepleting period (note: this period only applies to subjects who received lymphodepleting chemotherapy)	From the first day of lymphodepleting chemotherapy • to the day before infusion of tisagenlecleucel, for subjects who received infusion, or • to the earlier of date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy for subjects who didn't receive infusion of tisagenlecleucel	All subjects who received lymphodepleting chemotherapy
Post-infusion period	Starting at day of first tisagenlecleucel infusion until end of study	Safety set/Infused set

2.8.2 Adverse events (AEs)

The adverse events 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 4.03The grading of CRS will be based on protocol specific grading scales (Protocol Section 6.2.6.1).

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. the ***tisagenlecleucel-treatment-emergent*** AEs.
AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (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 preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables. The frequency of AEs of CTC grade 3 or above will be summarized together.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their descending frequency in the 'All grades' column.

For the **safety post tisagenlecleucel infusion**, the following adverse event summaries will be produced on post-infusion period by timing of onset: Within 8 weeks post first tisagenlecleucel

infusion, 8 weeks to 1 year post first tisagenlecleucel infusion, >1 year post first tisagenlecleucel infusion, and any time post first tisagenlecleucel infusion. The denominator for each time period will be the number of subjects still remain in study at the start of the corresponding time period.

- Overview of adverse events , deaths, and other serious or clinically significant AEs
- Adverse events, regardless of tisagencelleucel relationship, by primary system organ class, preferred term
- Adverse events, suspected to be tisagenlecleucel related, by primary system organ class, preferred term
- Serious adverse events, regardless of tisagenlecleucel relationship, by primary system organ class and preferred term
- Serious adverse events, suspected to be tisagenlecleucel related, by primary system organ class and preferred term
- Non-Serious Adverse events, regardless of tisagenlecleucel relationship, by primary system organ class and preferred term

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 or lymphodepleting period will be also summarized separately for enrolled subjects and subject who received lymphodepleting chemotherapy respectively.

2.8.2.1 Adverse events of special interest / grouping of AEs

AESIs include all important identified and potential risks of tisagenlecleucel, and may also include additional relevant safety topics (e.g. missing information or exploratory safety topics). 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 and will be provided in a listing. For the **safety post tisagenlecleucel infusion**, AESIs will be summarized by drug relationship, group term, preferred term, and timing of onset: Within 8 weeks post first tisagenlecleucel infusion, 8 weeks to 1 year post first tisagenlecleucel infusion, >1 year post first tisagenlecleucel infusion, and any time post first tisagenlecleucel infusion. AESIs will also be listed.

2.8.2.1.1 Cytokine release syndrome

Detailed information regarding the first episode of CRS, including maximum CRS grade, time to onset of CRS; duration of CRS, time to Grade 3/4/5 CRS, concurrent infections, [redacted] will be summarized.

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, end of study evaluation date and death date (if applicable). Time to CRS onset and time to high fever (temperature >38 °C or ≥ 100.4 degrees Fahrenheit) onset will be plotted against the maximum CRS grade using strip plot as appropriate.

2.8.2.1.2 Serious neurological events

Serious 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 day and the start day 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 unresloved. Time to onset of the first serious neurological event episode will be summarized descriptively. Time to resolution of all serious neurological event episodes from all subjects will be summarized using KM method by ignoring the fact that multiple episodes might be clustered by subject. That is, for one subject, if there are 2 episodes, both episodes are included in the KM analysis. Though the 2 episodes for one subject are not completely independent, they are treated as if they are from two subjects (each with 1 episode).

2.8.2.2 Deaths

Summary tables for deaths will be produced by system organ class and preferred term.

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

All deaths will be listed, period as defined in Section 2.8.1 will be flagged in the listings.

2.8.3 Laboratory data

For laboratory tests covered by the CTCAE, the study's biostatistics and reporting team will grade laboratory data accordingly. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

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

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

For the **safety post-tisagenlecleucel infusion**, the shift tables for tisagenlecleucel arm will be generated by timing: Within 8 weeks post first tisagenlecleucel infusion, >8 weeks to 1 year post first tisagenlecleucel infusion, >1 year post first tisagenlecleucel infusion, and any time post first tisagenlecleucel infusion.

In addition, percentage of subject with Grade 3 or 4 hematopoietic cytopenias 28 days post tisagenlecleucel infusion will be summarized. Among subjects with Grade 3 or 4 hematopoietic cytopenias 28 days post tisagenlecleucel infusion, the timing of resolution to Grade 2 or below will be summarized via Kaplan-Maier method. Grading of cytopenias will be derived using lab results in absolute lymphocytes (hypo), absolute neutrophils (hypo), hemoglobin (hypo),

platelet count (hypo) or WBC (hypo) according to CTCAE 4.03. If a subject did not achieve resolution at the last lab assessment, timing of resolution will be censored at the last assessment. The median time to resolution and KM estimates of % resolved cases at different time point (month 2, month 3 and etc.) will be summarized.

Key laboratory abnormalities of CTC grade 3 or 4 will be listed with the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

Hematopoietic cytopenias not resolved by Week 4

For hematopoietic cytopenias not resolved by Week 4 (defined as day 35, i.e. day 28 +7days time-window for day 28 visit), analysis on laboratory results will be performed. Infections started on or after day 28 among subjects with grade 3 or above neutropenia not resolved by day 28 per lab results will be listed.

Liver function parameters

Liver function parameters of interest are total bilirubin (BILI), ALT, AST and alkaline phosphatase (ALP). The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- BILI > 2xULN
- BILI > 3xULN
- ALT or AST > 3xULN & BILI > 2xULN
- ALT or AST > 3xULN & BILI > 2xULN & ALP ≥ 2xULN
- ALT or AST > 3xULN & BILI > 2xULN & ALP < 2xULN

A time window of 8 weeks will be considered while deriving summaries for combined elevations, This lag time will be applied irrespective of the sequence (i.e., AST/ALT first or TBL first).

2.8.4 Immunogenicity

2.8.4.1 Humoral immunogenicity

Humoral immunogenicity assessment will include prevalence of immunogenicity (subjects with pre-existing antibodies that bind to CTL019) and incidence of immunogenicity (subjects with treatment-induced or treatment-boosted antibodies that bind to CTL019), together with antibody titers.

The proportion of humoral immunogenicity positive and negative subjects will be summarized by time points. Summary statistics will be presented for CTL019 cellular kinetic parameters for

qPCR by anti-CTL019 antibody post-infusion status (positive or negative) on the Cellular kinetic analysis set (CKAS). If the value of Signal (MFI) of anti-mCAR19 antibodies is greater than 2.28 times higher than the enrollment value at any time post-baseline and the enrollment value is positive the patient is anti-mCAR post-infusion positive. If the enrollment value is negative, the patient is post-infusion positive if any post-baseline value is positive. If there is no available baseline or post-baseline category, the post-infusion immunogenicity will be considered unknown and these patients will be summarized separately.

A scatter plot of baseline and post-baseline anti-CTL019 antibodies versus qPCR AUC0-28d and Cmax will be presented along with the appropriate regression line and equation on the CKAS. In addition boxplots of anti-CTL019 antibodies at enrollment by BOR and max CRS grade will be presented on the EAS and safety set, respectively. The same response categories will be used for a similar boxplot summarizing the maximum fold change of anti-CTL019 post-infusion.

The impact of maximum fold change of anti-mCAR19 antibodies post-infusion on DOR and PFS will be explored using a cox regression model using log of maximum fold change as a covariate using the EAS. The hazard ratio and 95% confidence interval for a doubling of the maximum individual fold change will be displayed. In addition Kaplan-Meier plots of DOR and PFS by quartiles of maximum fold change in antibodies and induced or boosted immunogenicity post-infusion will be displayed.

The geometric mean and arithmetic mean concentration time profiles of CTL019 by qPCR will be displayed by anti-mCAR19 status for all patients (tisagenlecleucel infused set).

2.8.4.2 Cellular immunogenicity

The cellular immunogenicity will be summarized by time points.. The boxplot of maximum fold change of cellular immunogenicity by BOR will be presented on the EAS. The scatter plot of maximum fold change versus qPCR AUC0-28d and Cmax will also be presented along with the appropriate regression line and equation on the CKAS.

2.8.5 Other safety data

Vital signs will be collected as clinically needed. Presence of detectable RCL will be tested by VSV-G at protocol scheduled assessments and listed. Other relavant safety data will be listed.

2.9 Pharmacokinetic endpoints

Tisagenlecleucel concentrations in peripheral blood and bone marrow will be listed, graphed and summarized (arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum) by time points as assessed by the following:

- tisagenlecleucel transgene levels as measured by qPCR
- tisagenlecleucel transduced cells measured by flow cytometry of CD3-positive/CD4-positive and CD3-positive/CD8-positive tisagenlecleucel transduced cells.

The cellular kinetic parameters listed in Table 10-1 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 BOR and Month 3 disease response. All concentrations below the limit of quantitation or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics. For the calculation of the cellular kinetic parameters, a zero value will be imputed for the values below the limit of quantification after the administration and prior to any above LOQ value during the expansion phase. The values below the limit of quantification during the elimination phase will not be imputed and will be considered as zero.

Table 2-3 Noncompartmental cellular kinetic parameters

Parameter	Definition
AUC0-28d and/or AUC0-84d	The 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)ss
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)
T1/2	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
Tlast	The last observed measureable timepoint after dose administration
Clast	The last observed concentration after dose administration)

Descriptive statistics of cellular kinetic parameters will be summarized by arithmetic and geometric means, standard deviation, CV%, CV% geometric mean, minimum, median and maximum. For Tmax and Tlast only minimum, median and maximum will be presented. Cellular kinetic parameters will also be summarized by CRS grade, Month 3 and best overall response for the IEAS or the EAS at the interim and primary analysis, respectively.

[redacted]

The following analyses wil be performed outside the CSR SAP and will be documented in a seperate report:

[redacted]

[redacted]

2.10 Patient-reported outcomes

Patient Reported Outcome (PRO), such as scores of health-related quality of life questionnaires FACT-Lym, EQ-5D-3L and SF-36v2 (acute form) will be assessed at screening, Month 3, Month 6, Month 12, Month 18, Month 24 and at the End of Study visit.

Summary scores will be generated by summing the item responses on the questions for each domain in accordance with the respective scoring method provided by the developers. Descriptive statistics (e.g. mean, median and frequency) and change from baseline of the summary scores of each domain will be provided for each post baseline time-point/window of assessment based on all available data at the time of the analysis. Waterfall plots may be produced to illustrate change from baseline scores or histograms to show distribution of responses overtime. The IEAS or EAS will be used for all analysis at the interim and primary analysis respectively.

2.10.1 FACT-Lym

The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lymph) consists of a general quality of life instrument (FACT-G) and a condition specific module Lym. The FACT-G has 27 statements that patients will need to endorse on a five-point scale (not at all, a little, somewhat, quite a bit, very much). The statements cover four subscales: Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), and Functional Well-Being (FWB). The Lym subscale (LymS) consists of 15 statements patients need to endorse on an identical five-point scale. In addition, the following three total scores will be computed: FACT-Lymphoma Trial Outcome Index (TOI): sum of PWB, FWB and LymS scores; FACT-G total score: sum of PWB, SWB, EWB and FWB scores; and FACT-Lymphoma total score: sum of PWB, SWB, EWB, FWB and LymS scores.

Descriptive statistics will be used to summarize the raw and change from baseline of the above summary scores for each post baseline time-point/window of assessment.

If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

Prorated subscale score = [Sum of item scores] x [number of items in subscale]÷ [number of items answered]

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc.). The total score is then calculated as the sum of the un-weighted subscale scores. In addition, a total score should only be calculated if all of the component subscales have valid scores.

2.10.2 EQ-5D-3L

The EQ-5D-3L is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one

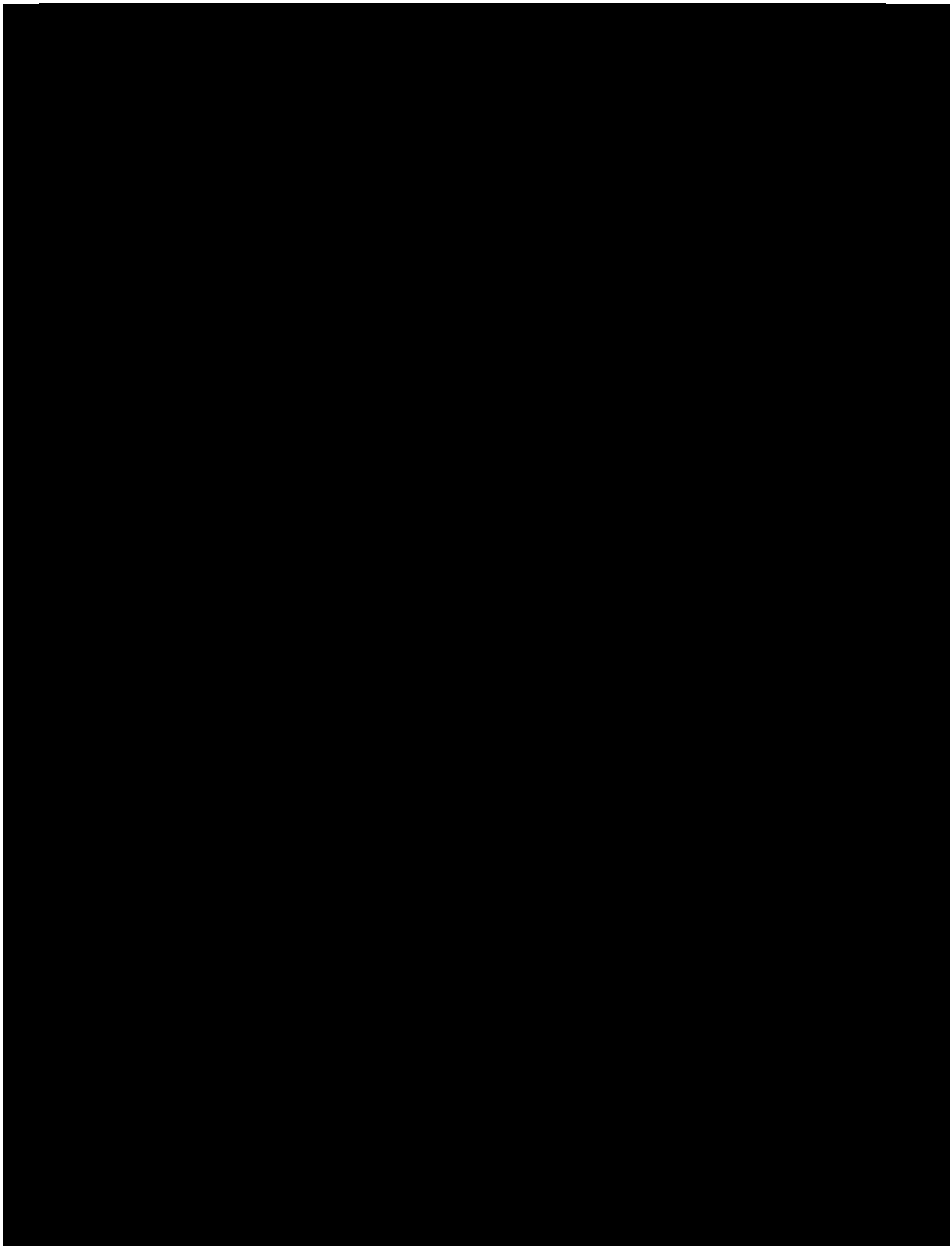
item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients report each of these items from "no problems", "some problems", or "extreme problems." The second section of the questionnaire (EQ-VAS) measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today," and the questionnaire requires 5 to 10 minutes to complete.

The EQ-5D-3L will be scored according to its scoring manual. For the EQ-5D health state profiles, the proportions of patients reported having "no", "some", or "extreme" problems at each time point will be reported for each of the 5 dimensions. Summary statistics and rate of improvement for EQ-VAS will be evaluated from baseline to each time point.

2.10.3 SF-36

The Short Form Health Survey (SF-36v2 (acute form)) contains 36 items which measure eight dimensions: Physical functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Two summary scores of physical and mental health can also be calculated. Item scores for each dimension are coded, summed and transformed to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). The higher values indicate a better evaluation of health. The scoring of the questionnaire will be provided by the vendor for this instrument.

Descriptive statistics will be used to summarize the raw and change from baseline of the above summary scores for each post baseline time-point/window of assessment.



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

The number and percentage of subjects enrolled,infused with tisagenlecleucel and discontinued during the pre-COVID-19 pandemic period, during 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.

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

- Pre-pandemic set: Subjects who completed the treatment and follow-up period or discontinued the trial before the pandemic start date in their region/country.
- During pandemic set: Subjects with at least one on-treatment assessment or treatment-emergent event during the pandemic dates as defined for their region/country.
- After-pandemic set: Subjects who were enrolled (based on the screening completion date) in the study after the pandemic end date in their region/country.

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

Listing of suspected or confirmed SARS-CoV-2 infections will be presented. Additionally, concomitant medications will be listed separately for subjects infected with COVID-19.

2.14 Interim analysis

One interim analysis for overwhelming efficacy is planned for the study when approximately 50 patients of the planned 90 (55.6%) have received tisagenlecleucel infusion and have either completed 6 months from study day 1 infusion or discontinued earlier. An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in EAST 6.3, will be used to construct the efficacy stopping boundary (Lan and DeMets 1983). Based on this choice of α-

spending function, if the interim analysis is performed with 50 patients, the lower bound of the 2-sided 99.48% exact confidence interval for CRR will need to be greater than 15% to declare statistical significance. As a result, a CRR of 16/50=32% will be needed to claim success at interim analysis. At the final analysis when 90 patients are treated and followed for at least 6 months, 2-sided 95.16% exact CI will be used correspondingly, requiring an CRR of 21/90=23.3% to claim success.

In case the actual number of patients included in the interim analysis cut-off date is not exactly equal to the planned 50 patients, the efficacy boundaries will be re-calculated based on the actual number of patients using the pre-specified α-spending.

By the time of the interim analysis, all patients are expected to have been treated. Therefore, the study will not be stopped for outstanding efficacy regardless of the interim analysis results.

3 Sample size calculation

The observed CRR was 14% in a recent study of idelalisib-treated patients with relapsed or refractory follicular lymphoma (Salles et al 2017).

Based on the null hypothesis of CRR ≤ 15% and assuming the underlying CRR of 30% for tisagenlecleucel, 90 patients in the primary analysis will provide at least 90% cumulative power to demonstrate statistical significance, using a 2-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary and an exact confidence interval at one-sided cumulative 0.025 level of significance, if the underlying CRR is 30%. In this setting, a CRR of 21/90=23.3% will be needed to claim success.

Assuming 20% enrolled patients will not be infused due to reasons such as manufactory failure, worsening of patient's condition, etc., at least 113 patients need to be enrolled to ensure 90 patients are treated and hence will be used for the primary analysis.

4 Change to protocol specified analyses

No change from protocol specified analyses was made.

- The "Full analysis set" was renamed as "Tisagenlecleucel infused set" for clarity.
- The censoring reason "Event documented after at least 2 missing tumor assessments" for the analysis of the secondary endpoints DOR and PFS has been removed. Disease progression or death after 2 or more tumor missing assessments will be counted as event following standard project rule and assuming that missing assessments are unlikely to correspond to disease progression in follicular lymphoma.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE, Concomitant medication, and safety assessment date imputation

Table 5-1 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 5-2 Imputation of end dates (AE)

Missing Element	Rule
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY and end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

*End date of the on-treatment period = min(end of study visit date, death date, data cut-off date, withdrawal of consent 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.

5.1.3 Prior anti-neoplastic 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.

5.1.4 Other imputations

Incomplete date of initial diagnosis of cancer, first relapse and date of most recent relapse/progression

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 date of best response to last line of prior anti-neoplastic therapy

If the day of best response to last line is missing, the day will be imputed to the minimum (progression date -1, last day of the month).

Date of hospitalization imputation

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

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Note: The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in the Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE version 4.03, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

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.

5.4 Statistical models

5.4.1 Primary analysis

The following statistical hypothesis will be tested using a one-sided test with α=0.025 based on the exact binomial distribution:

H_0: CRR ≤ 15% will be tested vs H_1: CRR > 15%.

Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (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*)) two-sided Pearson-Clopper CI and exact one-sided p-value for the hypothesis test of the *null proportion* (0.15).

5.4.2 Key secondary analysis

There is no key secondary analysis.

5.5 Independent Review Committee

For analysis per IRC data, the response assessment by oncology review should be considered.

5.6 Time windows

Table 5-3 shows the defined time windows for patient reported outcome.

If more than one assessment is done within the Baseline time window, the assessment closest to and before the infusion date will be used.

For all other time windows,

- if two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to the scheduled visit will be considered;if more than one assessment is done at a specific timepoint, the average of available item responses will be used for the analyses. For questionnaires with categorical outcomes, the assessment which falls into the planned visit will be used.

Table 5-3 Time windows for patient reported outcome

Time Window	Planned visit timing (study day)	Time Window Definition (Study days)
W-10 to W-6 (Baseline)	Before or on Day 1	Last one on or before tisagenlecleucel infusion date
M3±14d	91	60 to 136
M6±14d	183	137 to 228
M9±14d	274	229 to 319
M12±14d	365	320 to 456
M18±14d	548	457 to 639
M24±14d	731	640 to 913

Study Day 1 = start date of tisagenlecleucel infusion

5.7 Endpoints derivation

5.7.1 PFS from enrollment

PFS for non-infused enrolled subjects

For non-infused patients who were enrolled in the study PFS is the time from enrollment to the earliest of the following:

- Death from any cause
- Disease progression
- New anticancer therapy including bridging therapy

For all other patients the PFS will be censored at day 1 (i.e. enrollment date).

PFS for infused subjects for Enrolled set

Use the information from the analysis dataset and use enrollment date as the starting point instead of infusion start date to calculate PFS from enrollment.

5.7.2 OS from enrollment

For all patients who were enrolled in the study OS is the time from enrollment to date of death due to any reason. If a death has not been observed by the date of analysis cutoff, OS will be censored at the date of last contact.

6 References

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