NOVARTIS

Clinical Development

CTL019

Oncology Clinical Protocol 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

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Table of contents

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[redacted]

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List of figures

List of tables

[redacted]

[redacted]

List of abbreviations

ABC	Activated B-cell
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
AESI	Adverse events of special interest
Alb	Albumin
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
ASH	American Society of Hematology
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
ATC	Anatomical Therapeutic Chemical
ATG	Anti-thymocyte Globulin
ATP	Adenosine 5'-triphosphate
AUC	Area Under the Curve
AV	Atrioventricular
Bcl	B-cell lymphoma
Bcl-6	B-cell lymphoma 6 protein
BCR	B cell receptor
BiPAP	Bilateral Positive Airway Pressure
bpm	beat per minute
BTK	Bruton’s Tyrosine kinase
BUN	Blood Urea Nitrogen
CAR	Chimeric antigen receptor
CBC	Complete Blood Count
CCG	CRF Completion Guidelines
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CGD	Chronic granulomatous disease
CI	Confidence Interval
CIF	Cumulative incidence function
CKAS	Cellular Kinetic Analysis Set
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
Cmax	Maximum concentration
CMV	Cytomegalovirus
c-myc	c-mycproto-oncogene
CMR	Complete Metabolic Response
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CR	Complete Response
CRi	Complete Response with incomplete bone marrow recovery
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization

[redacted]

CRP	C-Reactive Protein
CRR	Complete Response Rate
CRS	Cytokine Release Syndrome
CSF	Cerebral spinal fluid
CSP	Clinical Study Protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTL	Cytotoxic T-lymphocyte
CV	Coefficient of Variation
CYP	Cytochrome P
DLBCL	Diffuse large B-cell lymphoma
DFS	Disease free survival
DLT	Dose Limiting Toxicity
DMC	Data monitoring committee
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
EC	European Community
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event free survival
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End Of Study
EQ-5D-3L	European Quality of Life-3 Dimensions
ESMO	European Society for Medical Oncology
EU	European Union
FACT-G	The Functional Assessment of Cancer Therapy – General
FACT-Lym	The Functional Assessment of Cancer Therapy - Lymphoma
FAS	Full analysis set
FDA	Food & Drug Administration
FDG	Fluorodeoxyglucose
FFP	Fresh frozen plasma
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FNA	Fine Needle Aspirate
FPFV	First Patient First Visit
g	gram

[redacted]

GC	Germinal center-like
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GELF	Groupe d'Etude des Lymphomes Folliculaires
GM-CSF	Granulocyte macrophage-colony stimulating factor
GVHD	Graft versus Host Disease
HA	Health Authority
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HR	Heart Rate
HSCT	Hematopoietic stem cell transplant
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
[redacted]	[redacted]
Ig	Immunoglobulin
IgH	Immunoglobulin heavy locus
IL	Interleukin
IL6R	Interleukin 6 receptor
IN	Investigator Notification
INR	International Normalized Ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IT	Intrathecal
ITP	Autoimmune thrombocytopenia/thrombocytopenic purpura
IUD	Intrauterine Device
i.v.	Intravenous(ly)
IWRS	Interactive Web Response System
JCV	John Cunningham Virus
Kg	Kilogram
Ki67	The murine cell proliferation antigen
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LFT	Liver function tests
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
LPLV	Last Patient Last Visit
LSS	Lymphoma Specific Survival
LTFU	Long Term Follow Up
LTR	Long Terminal Repeat

[redacted]

LVEF	Left Ventricular Ejection Fraction
MAP	Master Analysis Plan
MAS	Macrophage Activation Syndrome
MedDRA	Medical Dictionary for Regulatory Authorities
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MCL	Mantle Cell Lymphoma
mRNA	messenger RNA
mg/m^2	milligram per square meter
MHC	Major histocompatibility complex
min	minutes
mL	milliliter
MNC	Mononuclear cell
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MTX	methotrexate
MUGA	Multiple Uptake Gated Acquisition
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NE	Norepinephrine Equivalent
NE	Not Evaluable
NFkB	Nuclear Factor-kappa B
NHL	Non-Hodgkin's Lymphoma
NK-cell	Natural Killer cell
NOS	Not otherwise specified
NR	No Response
NYHA	New York Heart Association
O_2	Oxygen
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive disease
PD	Pharmacodynamics
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death ligand-1
PE	Physical Examination
PET	Positron emission tomography
PFS	Progression Free Survival
PGS-CRS	The Penn Grading Scale for Cytokine Release Syndrome
PHI	Protected Health Information
PI	Principal Investigator
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PMBCL	Primary mediastinal large cell lymphoma
PML	Progressive Multifocal Leukoencephalopathy
PMR	Partial Metabolic Response

[redacted]

PPS	Per Protocol Set
PR	Partial Response
PRi	Partial Response with incomplete bone marrow recovery
PRO	Patient Reported Outcome
PT	Preferred Term
PT	Prothrombin time
PTLD	Post-transplant lymphoproliferative disorders
q3M	Quarterly (every 3 months)
QA	Quality Assurance
QOL	Quality of Life
qPCR	Quantitative Polymerase Chain Reaction
R/D	Relapsed Disease
r/r	Relapsed or refractory
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RDE	Recommended dose for expansion
REB	Research Ethics Board
RNA	Ribonucleic acid
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
scFv	Single chain variable fragment
SCID-X1	X-linked Severe Combined Immunodeficiency
SD	Stable Disease
SD	Standard Deviation
SF-36	Short Form 36 health survey
SGOT	Serum glutamic-oxaluacetic transaminase
[redacted]	[redacted]
SGPT	Serum glutamic-pyruvic transaminase
SMQ	Standard medical query
SOC	System Organ Class
SPD	Sum of the product of the diameters
SUSAR	Suspected unexpected serious adverse reactions
TBL	Total Bilirubin
TCR	T cell receptors
TKI	Tyrosine Kinase Inhibitor
TLS	Tumor lysis syndrome
Tmax	Time to peak concentration
TNC	Total nucleated cells
TNF	Tumor Necrosis Factor
[redacted]	[redacted]
TTP	Time to progression
TTR	Time to Response
UK	United Kingdom
ULN	Upper Limit of Normal

[redacted]

ULOQ	Upper Limit of Quantification
UNK	Unknown
UPENN	University of Pennsylvania
US	United States
VASST	Vasopressin and Septic Shock Trial
V_H	Heavy Chain Variable Domain
V_L	Light Chain Variable Domain
VSV-g	Vesicular Stomatitis Virus, Glycoprotein
WAS	Wiskott-Aldrich syndrome
WBC	White blood cells
WHO	World Health Organization
yGT	Gamma glutamyl-transpeptidase

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Baseline Efficacy Assessment	If multiple assessments are performed prior to infusion then the one closest temporally prior to infusion will serve as baseline assessment.
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Final Enrollment	Point/time of patient entry into the study when the following have been confirmed: A. ICF signed B. Local patient eligibility completed C. Leukapheresis product received and accepted for manufacturing
HSCT	Hematopoietic stem cell transplantation (HSCT) refers to both allogeneic HSCT and autologous HSCT
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Treatment whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial SAP documentation
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Patient (subject) information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later

[redacted]

Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including lymphodepleting chemotherapy. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Subject Number	A unique identifying number assigned to each patient (subject) who enrolls in the study
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further collection of personal data

[redacted]

Protocol summary:

Full title	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
Brief title	Efficacy and safety of tisagenlecleucel in adult patients with refractory or relapsed follicular lymphoma
Sponsor and clinical phase	Novartis, Phase II
Investigation type	Biological
Study type	Interventional
Purpose and rationale	Despite recent progress, follicular lymphoma (FL) remains incurable. A recent analysis showed that FL patients who relapsed within 2 years of R-CHOP therapy (approximately 20% of all patients) had poor prognosis, with a 5-year OS of 50% versus 90% in those who relapsed later (Casulo et al 2015). These data challenge the indolent behavior of FL and emphasize the need for novel therapies. CD19 represents an attractive therapeutic target because it is widely expressed on malignant B-cells, including FL (Freedman 2014). Tisagenlecleucel consists of autologous T cells that are genetically modified ex vivo via lentiviral transduction to express a chimeric antigen receptor (CAR) consisting of a CD19 antigen recognition domain attached to intracellular signaling domains that mediate T-cell activation. Data from patients with B-cell acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and DLBCL show a potent anti-tumor activity of tisagenlecleucel. In Study A2101J, 14 patients with refractory FL were infused with tisagenlecleucel. Ten (71%) patients achieved CR and maintained it after 28.6 months of follow up (Schuster et al 2017).
Primary objective	Evaluate the efficacy of tisagenlecleucel therapy as measured by complete response rate determined by Independent Review Committee in the full analysis set based on Lugano 2014 classification response criteria (Cheson et al 2014).
Secondary objectives	• Evaluate the efficacy of tisagenlecleucel as measured by additional efficacy measures, including Overall Response Rate (ORR), Duration of Response (DOR), Progression Free Survival (PFS) and Overall Survival (OS). • Evaluate safety of tisagenlecleucel • 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 • Characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) • Characterize the impact of pre-existing and treatment induced immunogenicity on cellular kinetics, efficacy and safety • Describe the effect of tisagenlecleucel therapy on patient reported outcomes
Study design	Single arm, multi-center, phase II study to determine the efficacy and safety of tisagenlecleucel in adult patients with relapsed or refractory FL with the following sequential phases: Screening, Pre-treatment, Treatment and Follow-up. Efficacy and safety will be evaluated for 2 years post-infusion. Afterwards, patients will continue to be followed until 15 years post-infusion as per health authority guidelines in a separate study protocol.
Population	Approximately 113 adult patients with relapsed or refractory FL will be enrolled to obtain 90 patients treated with tisagenlecleucel.
Key inclusion criteria	Patients eligible for inclusion in this study have to meet all of the following criteria (for detailed criteria see Section 5.2):

[redacted]

	• Written informed consent prior to any screening procedures
	• ≥18 years of age at the time of ICF signature
	• FL (Grade 1, 2, 3A) confirmed histologically by central pathology review before tisagenlecleucel infusion.
	• FL meeting one of the following criteria:
	  ○ Refractory to a second line or later line of systemic therapy (including anti-CD20 antibodies and alkylating agents) or relapsed within 6 months after completion of a second line or later line of systemic therapy
	  ○ Relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion
	  ○ Relapsed after autologous HSCT
	• Radiographically measurable disease at screening

Key Exclusion criteria	Patients eligible for this study must not meet any of the following criteria: • Evidence of histologic transformation • Follicular Lymphoma Grade 3B • Prior anti-CD19 therapy • Prior gene therapy • Prior adoptive T cell therapy • Prior allogeneic hematopoietic stem cell transplant • Active CNS involvement by malignancy
Study treatment	The recommended dose will consist of a single intravenous (i.v.) infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.
Efficacy assessments	• Radiologic imaging by PET and CT (or MRI, if CT contraindicated) • Bone marrow biopsy or aspirate • Tumor biopsy or cytology
Key safety assessments	• Vital signs • Adverse events • Laboratory tests
Pharmacodynamic assessments	[redacted] • B cell and T cell levels (peripheral blood), [redacted]
Pharmacokinetic assessments	Tisagenlecleucel cellular kinetics by q-PCR and flow cytometry
Other assessments	• Leukocyte gene expression profiling • Flow cytometry of peripheral blood before leukapheresis • Flow cytometry of leukapheresis product • Patient reported outcomes (SF-36v2, FACT-Lym, and EQ-5D-3L)
Data analysis	The primary endpoint is the complete response rate as determined by independent review committee (IRC). The complete response rate 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. One interim analysis for overwhelming efficacy is planned for the study when approximately 50 patients of the planned 90 (55.6%) have received infusion and have either completed 6 months from study day 1 infusion or discontinued earlier. The primary analysis will be performed when 90 patients have received infusion and completed 6 months from study day 1 infusion or discontinued earlier.

[redacted]

	The primary efficacy analysis will be performed by testing the null hypothesis of complete response rate being less than or equal to 15% at one-sided cumulative 2.5% level of significance. The complete response rate will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. P-value from binominal exact test will be provided.
Key words	Refractory/relapsed, follicular lymphoma, CTL019, tisagenlecleucel

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of lymphoid malignancies, including immature lymphoid neoplasms, mature B-cell neoplasms, mature T-cell and NK-cell neoplasms, and post-transplant lymphoproliferative disorders (Swerdlow et al 2008). Mature B-cell lymphomas are further classified into indolent lymphomas, e.g. follicular lymphoma (FL), and aggressive lymphomas, e.g. diffuse large B-cell lymphoma (DLBCL).

FL is the second most common histologic NHL subtype in the Western hemisphere (Ghielmini et al 2013). The estimated number of new cases in the US was 13,960 in 2016 (Teras et al 2016). Most patients are diagnosed during the sixth decade of their life but approximately 25% of patients are 40 years of age or younger (Jaglowski et al 2009). The translocation t(14;18)(q32;q21) is the genetic hallmark of follicular lymphoma, which results in the constitutive overexpression of B-cell lymphoma 2 protein (Bcl-2). FL cells also express surface immunoglobulins, B-cell lymphoma 6 protein (Bcl-6), and B-cell associated antigens such as CD10, CD19, CD20, and CD22. FL is classified histologically into three grades based on the number of centroblasts (Swerdlow et al 2008).

Most FL patients have widespread disease at diagnosis, including peripheral and central lymph nodes, spleen and bone marrow. Current therapeutic approaches include “watchful waiting”, radiotherapy, radioimmunotherapy, and anti-CD20 monoclonal antibodies with or without chemotherapy. Follicular lymphoma frequently relapses and therefore is considered incurable. Patients relapsing within 2 years of therapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), presenting approximately 20% of cases, have a poor prognosis with a median 5-year survival of only 50% (Casulo et al 2015).

The management of relapsed or refractory FL (r/r FL) includes non-cross resistant agents, autologous/allogeneic hematopoietic stem cell transplantation (HSCT), and phosphatidylinositol 3-kinase (PI3K) inhibitors, such as idelalisib and copanlisib. PI3K plays a critical role in the B-cell receptor pathway and is overexpressed in B-cell malignancies. Both idelalisib and copanlisib are approved for the treatment of FL that relapsed after at least two prior systemic therapies based on single arm, open label, phase 2 studies. In idelalisib-treated FL patients, overall response rate (ORR) was 56%, including 14% with complete response (CR) and 42% with partial response (PR), while median progression free survival (PFS) was 11.0 months (Salles et al 2017). In copanlisib-treated FL patients, ORR was 59% (CR 14%, PR 44%), and median PFS was 12.2 months (FDA 2017).

Autologous HSCT does not result in significant overall survival benefit in patients with relapsed FL when compared to those treated with salvage chemoimmunotherapy (Epperla et al 2017). Allogeneic HSCT, a potentially curative therapy, is eligible for a very small number of selected patients. Moreover, it leads to high transplant-related mortality of 8-17% at 1 year (Epperla et al 2017).

Tisagenlecleucel is an adoptive cellular immunotherapy that uses autologous peripheral blood T cells that have been genetically modified ex vivo to target CD19 on the surface of B cells.

[redacted]

Recent studies indicate that tisagenlecleucel is highly effective in B cell malignancies, including r/r FL, where high CR rates and long duration of response are seen (Schuster et al 2017).

1.1.1 Historical experience with retroviral gene therapies

Retroviral vectors are useful gene delivery vehicles because they insert a deoxyribonucleic acid (DNA) copy of their genome into the host cell. However, insertion of vector sequences has the potential to up-regulate, dysregulate, or knockout local gene expression, which theoretically may lead to insertional oncogenesis. Malignant cell transformation after vector-mediated insertional mutagenesis has been observed in X-linked severe combined immunodeficiency (SCID-X1), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome (WAS) where first-generation gamma-retroviral vectors harboring long terminal repeats (LTRs) with strong enhancer/promoter sequences were used (Hacein-Bey-Abina et al 2003, Howe et al 2008, Boztug et al 2010, Stein et al 2010, Persons and Baum 2011).

Lentiviral vectors, a major subset of retroviral vectors, demonstrate distinct integration patterns compared to oncoretroviral vectors, which have been the predominant vector to date for gene transfer studies. The integration pattern of lentiviral vectors tends to be inside active transcription units as opposed to upstream in the locus control region where the insertion would have a greater chance of up-regulating gene expression. In addition, lentiviral vectors have no enhancer activity in their LTR regions and have lower levels of poly-A read-through, all factors which may improve gene transfer safety (Zaiss et al 2002). Thus, lentiviral vectors appear a safer alternative to oncoretroviral vectors, which is supported by animal models (Montini et al 2006). Importantly, despite a very high transduction efficiency achieved using lentiviral vectors, molecular clonality studies have not indicated any reasons for concern, to date, in published clinical trials (Schambach et al 2013).

With the exception of a single study in neonatal mice, lentiviral vectors have not been shown to be oncogenic in nature (Themis et al 2005). A study in tumor prone mice demonstrated that lentiviral vector gene transfer into hematopoietic stem cells of up to an average of 6 copies per cell was not tumorigenic in contrast to retroviral vectors at an average copy number of 3 per cell (Montini et al 2006). It is notable that T cell leukemia is not a recognized side effect of human immunodeficiency virus (HIV) lentiviral infection.

A long-term retrospective study of >500 patient-years of collective patient samples tested for at least 11 years after infusion from three clinical trials using gamma-retroviral modified T cells did not show evidence of transgene silencing, atypical gamma-retroviral integration patterns, or clonal expansion (Scholler et al 2012). A favorable safety profile was also determined for a conditionally replicating HIV-derived lentivirus that delivered HIV envelope antisense to patient T cells. Moreover, no evidence for insertional mutagenesis or enrichment of vector copies near proto-oncogenes was observed after 21-36 months (Levine et al 2006) and 28-32 weeks (Wang et al 2009). Another group reported no apparent risk of vector related adverse events (AEs) following 263 infusions of autologous, lentiviral transduced T cells with a long ribonucleic acid (RNA) antisense to HIV-1 envelope (McGarrity et al 2013). More recently *ex vivo* lentiviral transduced hematopoietic stem cells were used to correct an inherited storage disease in three children and in an inherited WAS in 3 children with follow up for up to 24 months and 20-32 months, respectively. Lentiviral integration studies showed sustained gene marking with polyclonal engraftment of transduced cells with no evidence of aberrant clonal

[redacted]

expansion, no evidence of *in vivo* selection of clones carrying integrations near oncogenes and therefore no evidence of vector-induced genotoxicity (Biffi et al 2013, Aiuti et al 2013).

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of tisagenlecleucel

Adoptive T cell therapy for cancer involves the infusion of native or genetically modified mature T cells that have the capacity to recognize and eliminate the patient's malignant cells. In particular, chimeric antigen receptor-based approach involves engineering T cells with sequences that encode antibody-based antigen recognition moieties linked to signaling domains. Unlike T cell receptors (TCR), chimeric antigen receptors (CARs) allow the T cells to specifically target and destroy tumor cells in a Major Histocompatibility Complex (MHC) independent manner (Mellman et al 2011).

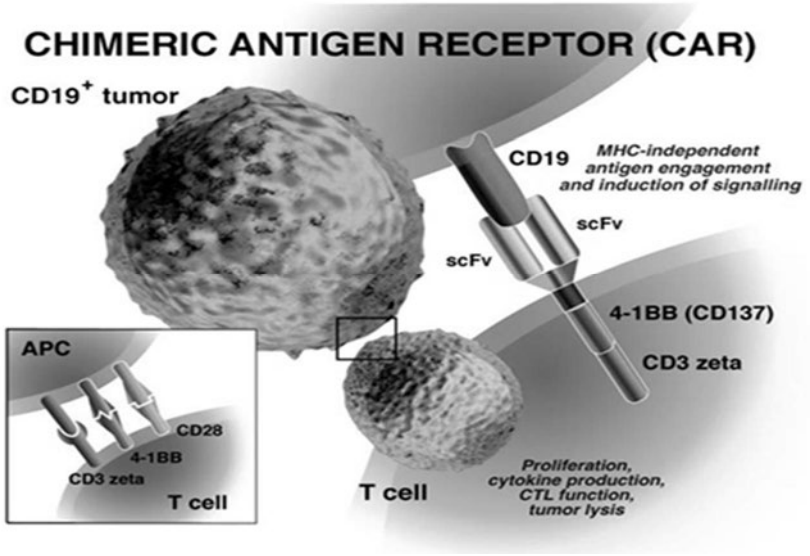
A promising target antigen for B cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors (Sadelain et al 2003, Porter et al 2011), with no expression on hematopoietic stem cells or non-B cell tissues. It is a member of the immunoglobulin (Ig) superfamily and a component of a cell surface signal transduction complex that regulates signal transduction through the B cell receptor (Fearon et al 2000). Mice lacking CD19 have decreased number of B cells in peripheral lymphoid tissues, decreased B cell response to oral vaccines and mitogens, and decreased serum Ig levels (Fearon et al 2000).

First generation CARs contain the TCR activation signal domain consisting of TCRζ. Second generation CARs contain costimulatory signaling domains as well: either CD28 or 4-1BB. The 3rd generation CARs contain further advancements such as double costimulatory modules comprised of CD28, 4-1BB plus TCRζ (June 2007, June et al 2009, Kohn et al 2011).

Tisagenlecleucel, a second generation CAR T cell therapy, is an adoptive cellular immunotherapy that uses the autologous peripheral blood T cells that have been genetically modified *ex vivo* to target CD19 on the surface of B cells. As shown in Figure 1-1, the CAR approach uses genetically programmed T cells transfected with chimeric receptor genes to combine the effector functions of T cells with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner (Gross et al 1989, Pinthus et al 2003). These receptors have the ability to recognize intact membrane proteins independent of antigen processing. The tumor antigen binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the heavy chain variable domain (V_H) and light chain variable domain (V_L) joined by a peptide linker of about 15 residues in length (Mullaney et al 2001).

[redacted]

Figure 1-1 Tisagenlecleucel chimeric antigen receptor design



Recent clinical trials of tisagenlecleucel in r/r CLL, r/r ALL, and r/r B cell lymphomas (including FL) have shown promising and durable anti-tumor efficacy (Porter et al 2011, Grupp et al 2013, Maude et al 2014, Schuster et al. 2017). Consequently, tisagenlecleucel appears to be a therapeutic alternative for patients with B cell malignancies (including FL) refractory to the current therapies. For further information refer to the [Investigator's Brochure].

1.2.2 Non-clinical experience

Extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models (Calogero et al 2000, Clay et al 2002, Hombach et al 2002, Pule et al 2003, Sadelain 2003). Others have used electroporation or retroviral vectors to create CAR T cells and have shown in vivo safety and efficacy of adoptively transferred T cells in immunodeficient mouse models (Willemsen et al 2000, Roessig et al 2002, Brentjens et al 2003, Cooper et al 2003, Serrano et al 2006). The incorporation of costimulatory signaling modules such as CD28 and 4-1BB in second generation CARs increases potency of the engineered T cells in pre-clinical studies (Finney et al 1998, Krause et al 1998, Eshhar et al 2001, Maher et al 2002, Finney et al 2004, Friedmann-Morvinski et al 2005, Brentjens et al 2010). The pre-clinical data supporting CAR T cell persistence, expansion and anti-tumor efficacy have been published (Gross and Eshhar 1992, Milone et al 2009).

1.2.3 Clinical experience

There are currently 12 ongoing therapeutic studies of tisagenlecleucel therapy (Study B2101J, Study B2205J, Study B2202, Study B2208J, Study B2203J, Study A2201, Study A2101J, Study C2201, Study ZUS01T, Study UPCC-19416 and Study UPCC-39416), three ongoing long term follow up safety studies (Study A2207J, Study A2208J, and A2205B), and two single patient IND studies (Z2101I and B2002I). In addition, there is one completed study B2102J which had the last patient's last visit on 06-Jul-2015. For more details on these studies please refer to the [Investigator's Brochure].

[redacted]

1.2.3.1 Clinical Cellular Kinetics

In adult r/r DLBCL patients from Study C2201, tisagenlecleucel typically exhibited an initial rapid expansion phase, achieving maximal expansion around Day 9 followed by a bi-exponential decline. The persistence of tisagenlecleucel transgene in peripheral blood has been observed for up to 18 months. All responding patients demonstrated expansion of transgene levels. Neither patient characteristics nor prior therapy had any clinically relevant impact on expansion Cellular and humoral immunogenicity had no impact on the cellular kinetics or clinical outcome (Awasthi et al 2017).

1.2.3.2 Clinical efficacy

Tisagenlecleucel is approved by the FDA for the treatment of patients up to 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse (Kymriah FDA 2017).

Tisagenlecleucel is being reviewed by the FDA and the EMA for the treatment of adult patients with refractory or relapsed DLBCL who are ineligible for autologous stem cell transplant, and by the EMA for the treatment of pediatric and young adult patients (age 3 to 25 years) with refractory or relapsed B-cell ALL.

Efficacy in r/r pediatric and young adult ALL

Out of the 63 tisagenlecleucel-infused patients, 52 (83%) achieved CR/CRi within 3 months after infusion, and all of them were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days (Kymriah FDA 2017).

Efficacy in adult r/r NHL

In Study C2201 (adult patients with r/r DLBCL), the overall response rate (ORR) was 53% (40% CR ad 14% PR), and 73.5% of the patients were relapse-free at 6 months of follow up. Most CR patients remained in CR at 3 months (Schuster et al 2017).

In Study A2101J, 14 patients with refractory FL were infused with tisagenlecleucel. Ten (71%) patients achieved CR and maintained it after 28.6 months of follow up (Schuster et al 2017).

1.2.3.3 Clinical Safety

Section 6.2.6 and Section 6.3.2 outline expected and potential toxicities related to tisagenlecleucel, most of which occur within 8 weeks of infusion.

Safety in r/r ALL

In patients with refractory or relapsed B cell precursor ALL, the most common adverse reactions were cytokine release syndrome (79%), hypogammaglobinemia (43%), infections-pathogen unspecified (41%), pyrexia (40%), decreased appetite (37%), headache (37%), encephalopathy (34%), hypotension (31%), bleeding episodes (31%), tachycardia (26%), nausea (26%), diarrhea (26%), vomiting (26%), viral infectious disorders (26%), hypoxia (24%), fatigue (22%), acute kidney injury (22%), and delirium (21%).

[redacted]

Eleven deaths were reported for patients who received KYMRIAH, of which 2 deaths occurred within 30 days of infusion. Seven were disease-related, three were attributed to infections, and one to intracerebral hemorrhage (Kymriah FDA 2017).

Safety in adult r/r B-NHL

In study C2201, among the 99 patients assessed for safety, there were 58% with CRS (15% Grade 3, 8% Grade 4), 21% with neurological events (8% Grade 3, 4% Grade 4), 34% with infections (18% Grade 3, 2% grade 4), and 1% with tumor lysis syndrome (Grade 3 only). The median time to CRS onset was 3 days (range 1-51 days), median CRS duration was 7 days (range 2-30 days); 15% of patients required tocilizumab and 11% of patients required corticosteroids.

There were 16 patients who died after tisagenlecleucel infusion. Three patients died within 30 days of tisagenlecleucel infusion due to DLBCL; 13 patients died more than 30 days (range from 41 to 236 days) after tisagenlecleucel infusion (12 due to DLBCL disease progression and 1 due to chronic kidney disease not related to tisagenlecleucel). Overall, the safety events that occurred in study C2201 were manageable with close monitoring and established treatment algorithm; the safety profile has been well characterized (Schuster et al 2017).

In a recent published study conducted at the University of Pennsylvania (study A2101J), 36 patients (20 DLBCL, 14 FL, 2 MCL) were treated with tisagenlecleucel. There was one death (possibly related to tisagenlecleucel) in a patient with FL who died 234 days after tisagenlecleucel infusion in pathological CR. For further information refer to the [Investigator's Brochure].

The recently approved CAR T cell therapy for adult r/r DLBCL caused CRS in 94% of patients (13% Grade ≥3) and neurologic toxicities in 87% of patients (31% Grade ≥3) (YESCARTA FDA 2017).

Vector-related Safety

To date, no vector-related AEs have been seen associated with higher tisagenlecleucel transgene levels of expression or persistence in three pediatric patients with r/r ALL and in 4 adult patients with r/r CLL.

Post-infusion monitoring for replication competent lentivirus (RCL) in trials with UPENN manufactured tisagenlecleucel therapy has shown no Vesicular Stomatitis Virus, Glycoprotein (VSV-G) by q-PCR detectable in any of the patient samples at time points up to 2 years following infusion (7 patients from UPCC03712 trial; 16 patients form UPCC04409 trial, 11 patients from CHP959 trial).

2 Rationale

2.1 Study rationale and purpose

Despite recent progress, FL remains incurable. A recent analysis showed that FL patients who relapsed within 2 years of R-CHOP therapy (approximately 20% of all patients) had poor

[redacted]

prognosis, with a 5-year OS of 50% versus 90% in those who relapsed later (Casulo et al 2015). These data challenge the indolent behavior of FL and emphasize the need for novel therapies.

CD19 represents an attractive therapeutic target because it is widely expressed on malignant B-cells but not on pluripotent stem cells or non-B cell tissues. CD19 is almost universally expressed in FL (Freedman 2014). Tisagenlecleucel consists of autologous T cells that are genetically modified *ex vivo* via lentiviral transduction to express a chimeric antigen receptor (CAR) consisting of a CD19 antigen recognition domain attached to intracellular signaling domains that mediate T-cell activation. Data from patients with B-cell acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and DLBCL show a potent anti-tumor activity of tisagenlecleucel.

In Study A2101J, 14 patients with refractory FL were infused with a single dose of CTL019 cells (range 1×10^8 to 5×10^8 CTL019 cells). Ten (71%) patients achieved CR and maintained it after 28.6 months of follow up (Schuster et al 2017).

The mechanism of action of tisagenlecleucel is independent of PI3K signaling. In addition, a cross-resistance with CD20-targeted therapies such as rituximab is not expected. Anti-CD19 CAR T cells are also effective in CLL patients who progressed on ibrutinib (Turtle et al 2017).

2.2 Rationale for study design

This single arm, multi-center, phase II study will determine the efficacy and safety of tisagenlecleucel in adult patients with FL who failed at least 2 prior systemic therapies, including an anti-CD20 antibody (e.g. rituximab) and an alkylating agent. Patients who were treated with other FL-targeting agents (including PI3K inhibitors) and patients who relapsed after autologous HSCT will also be included.

The rarity of r/r FL patients, poor prognosis, no established standard of treatment, low response rates to currently available therapies (see section 1.1), and a high response rate to tisagenlecleucel reported recently in heavily pretreated FL patients (Schuster et al 2017) justify a single-arm study design.

2.3 Rationale for dose and regimen selection

The recommended dose in this trial is a single infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells, which is based on data from studies in CLL, ALL and NHL. The dose-response, dose-safety, and dose-cellular kinetics analyses were performed using the data obtained from r/r DLBCL patients (data cut-off date: 8-March-2017) in Phase II study (Study C2201) to assess the impact of dose on exposure, response, and selected safety endpoints in order to select safe and efficacious doses for use in the prescribing setting (commercial) and Study E2202.

- Dose-response and dose-exposure: Across the dose range studied, dose and exposure were independent. Additionally, responses were observed across the full range of doses from 0.6 to 6.0×10^8 CAR-positive viable T cells.
- Dose-safety: The probability of any grade neurologic events and time to resolution of cytopenia were not impacted by dose. There was an increase in probability of any grade and grade 3/4 CRS with increasing dose; however, the probability of grade 3/4 CRS was comparable across the dose range of 5.0 to 6.0×10^8 CAR-positive viable T cells. The model estimates from logistic regression analysis showed that the probability of grade 3/4

[redacted]

CRS for dose of 5.0×10^8 cells and 6.0×10^8 cells were comparable, i.e., 0.389 and 0.462, respectively. In addition, CRS is generally manageable in the study with the steps outlined in the CRS algorithm.

Based on the totality of the dose-safety, dose-efficacy, dose-exposure and exposure-response, and considering the positive benefit risk observed across the full range of doses, the following recommended dose will be utilized for Study E2202: 0.6 - 6.0×10^8 CAR-positive viable T cells. Clinically meaningful responses were seen across this range in patients with r/r DLBCL in Study C2201.

In a recently published study conducted the the University of Pennsylvania, 14 DLBCL and 14 FL patients were infused with a median total tisagenlecleucel dose of 5.00 x 10^8 (range: 1.79 x 10^8 – 5.00 x 10^8). The CAR T cell specific toxicities, such as CRS and neurotoxicity were less frequent and less severe than previously reported for tisagenlecleucel in ALL and CLL (Schuster et al 2017).

For further information on tisagenlecleucel dosing in preclinical and clinical studies see [Investigator's Brochure].

2.4 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation (Dummer et al 2002), a finding that naive T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naive T cells are reduced below a certain threshold (Goldrath 1999, Surh 2000). Host lymphodepletion may enhance the effectiveness of adoptively transferred T cells (Dummer et al 2002). Homeostatic T cell proliferation can lead to activation of certain immune cell subsets (King et al 2004), providing a clue to improved anti-tumor responses. T cells can undergo up to seven rounds of cell division after being deprived of contact with antigen presenting cells (Kaech 2001, van Stipdonk 2001). Lymphodepletion eliminates regulatory T cells and other competing elements of the immune system that act as "cytokine sinks", enhancing the availability of cytokines such as IL-7 and IL-15 (Klebanoff et al 2005). Data indicates that the increased antitumor efficacy of adoptive transfer following host conditioning is more than simply "making room" because the quantitative recovery of adoptively transferred T cells in mice reveals that *in vivo* proliferation following adoptive transfer is identical in mice with or without previous irradiation (Palmer et al 2004).

Fludarabine with cyclophosphamide has been the most commonly utilized lymphodepleting regimen with CD19 CAR-T cell therapies. It has been demonstrated that addition of fludarabine to cyclophosphamide increases CAR-T cell expansion and persistence and improves disease free survival rates in adult patients with r/r B-ALL (Turtle et al 2016).

In studies [B2202] and [B2205J] combined data (cut-off dates: 24-Apr-2017 for Study [B2202]; 01-Feb-2016 for Study [B2205J]), 99 of 104 patients received lymphodepleting chemotherapy. Ninety-seven of these 99 patients received fludarabine and cyclophosphamide.

In study [C2201] 92 of 99 patients received lymphodepleting chemotherapy. Seventy-three patients received fludarabine and cyclophosphamide, and 19 received Bendamustine.

[redacted]

2.5 Rationale for choice of combination drugs

Not applicable

2.6 Rationale for choice of comparators drugs

Not applicable

2.7 Risks and benefits

Tisagenlecleucel administered to over 400 patients in clinical trials across the dose ranges tested has a well characterized safety profile in pediatric and adult patients with 14 patients with FL. Overall, it is anticipated that the benefits of tisagenlecleucel therapy, including complete and long-lasting remissions when compared to the current standards of care, will outweigh the risks in this study.

Appropriate eligibility criteria are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs are provided in Section 6.1.4 and Section 6.2.6.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and adherence to the recommendations for the management of AEs known to be occur with tisagenlecleucel exposure, and guidance for the investigators in the [Investigator's Brochure].

Safety risks that have been identified with the use of tisagenlecleucel or are considered potentially associated with tisagenlecleucel are briefly outlined below.

2.7.1 Identified safety risks

2.7.1.1 Cytokine release syndrome (CRS) / macrophage activation syndrome (MAS)

Cytokine release syndrome (CRS) is an on-target toxicity that is associated with tisagenlecleucel cell expansion, activation and tumor cell killing. It is a result of systemic inflammatory response caused when cytokines are released by activated T cells, including IFNg, IL-6 and TNF. Severe and life-threatening events have been observed in patients treated with tisagenlecleucel. In r/r B-ALL, these appeared to be related to tumor burden, early CRS onset and early fever onset. In DLBCL, the probability of developing grade 3 and 4 CRS was increased with high tisagenlecleucel dose and exposure. In the majority of cases, CRS occurs within the first two weeks post-infusion and shows a wide range of clinical signs and symptoms (Table 2-1). Macrophage activation syndrome (MAS) is also associated with CRS as manifested by liver function test abnormalities, cytopenias, and coagulopathy.

Life-threatening and fatal outcomes associated with CRS and severe concomitant infections have been observed in pediatric and adult patients treated with tisagenlecleucel.

[redacted]

Table 2-1 Clinical signs and symptoms associated with CRS (Lee et al 2014)

Organ system	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

A therapeutic strategy for the management of CRS is provided in Section 6.2.6.1 that should be followed.

2.7.1.2 Neurological events

Neurological events have been observed in patients following various types of T cell directed therapy including tisagenlecleucel and other CAR-T cell therapies of other institutions. The pathophysiology for neurotoxicity is not fully understood but thought to be related to generalized T cell mediated inflammation rather than direct toxicity of CAR-T cells on the brain (Tey 2014). Some of the neurological events observed may be related to CRS, but whether this results from systemic cytokines crossing the blood brain barrier and engaging cytokine receptors in the brain or from direct cytokine production in the CNS is not clear (Maus et al 2014). There are no clear predictors of neurologic toxicity.

Manifestations of neurological events may include a multifarious set of symptoms and diagnoses including agitation, altered state of consciousness, aphasia, confusion, delirium, disorientation, encephalopathy, headache, mutism, seizures or tremor. Some of the events are severe and may have a life-threatening outcome.

The majority of neurological events were observed within 8 weeks following tisagenlecleucel infusion and were transient, however a delayed onset (i.e.> 8 weeks) may occur.

Notably, the onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS. Onset of neurological events may be concurrent with high fever during the development and at the time of maximal grade of CRS. The incidence appeared to be greater with higher CRS severity, prior history of CNS leukemia, and history of other prior CNS diseases, and did not appear to be prevented by tocilizumab. Encephalopathy typically occurred after peak CRS symptoms and tended to be self-limiting with some exceptions. A few have occurred after CRS and were not associated with high fevers.

The causality assessment of neurological events in patients treated with tisagenlecleucel can be confounded as CNS toxicity may be associated with chemotherapy used for lymphodepletion and the presence of comorbid conditions such as CRS, fever and infections.

For the management of neurological events see Section 6.2.6.2.

[redacted]

2.7.1.3 Hypersensitivity including acute infusion reactions

Since tisagenlecleucel is an autologous cellular product, hypersensitivity may occur due to the excipients (such as dimethyl sulfoxide (DMSO) or dextran 40) of the infused solution in which the cells are dispersed. In addition, host immune responses may result from presentation of CAR transgene expressed immunogenic epitopes including murine sequences in the scFv extracellular binding domain (derived from a murine monoclonal antibody) or novel epitopes arising at junctions between components of the CAR fusion polypeptide (Park et al 2007; Lamers et al 2006; Lamers et al 2007; Lamers et al 2011).

Clinically, hypersensitivity reactions can be classified as 'immediate' or 'delayed' depending on their onset after drug administration (Corominas et al 2014; Limsuwan and Demoly 2010). *In principle*, immediate reactions including acute infusion reactions occur within less than 1 hour after drug administration and may present in a wide range of symptoms such as fever, chills, nausea, urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, bronchospasm, tachycardia, hypotension, anaphylaxis or anaphylactic shock. Delayed hypersensitivity reactions appear after more than 1 hour and up to several days after drug exposure and could include variable cutaneous symptoms such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens- Johnson syndrome, or drug reaction with eosinophilia and systemic symptoms (DRESS) (Averbeck et all 2007; Descotes 2012; Corominas et al 2014; Vultaggio et al 2016).

To date, the majority of events observed after tisagenlecleucel infusion were mild or moderate in severity, manageable and recovered.

Patients will have typically received lymphodepleting chemotherapy that is completed several days prior to tisagenlecleucel infusion. Therefore it should be kept in mind that symptoms and findings at this time may also be the result of the onset of chemotherapy related toxicities.

A therapeutic strategy for the management of hypersensitivity including acute infusion reactions is provided in Section 6.2.6.3.

2.7.1.4 Tumor lysis syndrome (TLS)

Tumor lysis syndrome (TLS) is a potentially life-threatening metabolic disorder that occurs when tumor cells undergo rapid decomposition spontaneously or in response to cytoreductive therapy. It tends to occur particularly with highly effective therapies and in patients with high tumor burden and cancers with a high potential for cell lysis include high-grade lymphomas, acute leukemias, and other rapidly proliferating tumors.

Metabolic abnormalities characteristic of TLS include abnormally high serum uric acid levels (hyperuricemia) resulting from the breakdown of purine-containing nucleic acids and major electrolyte imbalances such as hyperkalemia, hyperphosphatemia, and hypocalcemia. Delayed recognition of the metabolic imbalances caused by the massive release of tumor cell contents may result in clinical complications such as acute kidney injury, seizures, and cardiac arrhythmias (Mughal et al 2010).

Tumor lysis syndrome was clinically observed in a timely relation to tisagenlecleucel T cell expansion. In the clinical experience with tisagenlecleucel thus far, most cases of TLS had a

[redacted]

grade 3 in CTCAE severity, however, the risk has been moderate to low with appropriate monitoring after lymphodepleting chemotherapy, prophylaxis and treatment as needed.

A therapeutic strategy for the management of TLS is provided in Section 6.2.6.4.

2.7.1.5 Infections

There is an increased risk and severity of infections in patients with longer and more intense immunosuppression. Patients treated with tisagenlecleucel are at risk of infection for several reasons:

- Lymphodepleting chemotherapy prior to treatment with tisagenlecleucel may cause severe neutropenia and B-cell depletion from tisagenlecleucel itself is known to be associated with infections.
- B-cell depletion is known to be associated with hypogammaglobulinemia that also contributes to the risk.
- Patient with prolonged and profound immunosuppression may be at enhanced risk for more frequent and severe opportunistic infections
- Underlying bone marrow disease or dysfunction further increases the risk of infections

Serious infections were observed in patients after tisagenlecleucel infusion, some of which were life-threatening or fatal.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Hepatitis cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive, and also in patients who are HBsAg-negative but hepatitis B core antibody (anti-HBc) positive. HBV reactivation has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg-negative, anti-HBc-positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg-negative and anti-HBc-positive. Reactivation of HBV replication is often followed by hepatitis, as indicated by an increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Patients with active or prior hepatitis B, hepatitis C or HIV confirmed by serology will not be enrolled in the study; for detailed exclusion criteria see Section 5.2, for serology assessment see Appendix 2.

A therapeutic strategy for the management of infections is provided in Section 6.2.6.5.

2.7.1.6 Febrile neutropenia

Febrile neutropenia observed with tisagenlecleucel can be caused due to multiple factors, including underlying bone marrow disease, prior chemotherapies, radiation treatments or lymphodepleting chemotherapy, reduced response to growth factors (either exogenous or endogenous) in addition to B-cell aplasia that may favor a production of auto-antibodies binding

to the neutrophil surface resulting in neutropenia and also disturb the balance between granulopoiesis and lymphopoiesis in the bone marrow (Tesfa and Palmblad 2011).

Febrile neutropenia and associated events such as grade 3 or grade 4 decreased neutrophil counts with elevated temperature were reported in clinical studies with tisagenlecleucel. The use of chemotherapy is known to be associated with the risk of neutropenia and if severe, with febrile neutropenia. The risk of neutropenia depends on various factors such as type and dose of chemotherapy used, age, gender, performance status and baseline hematology lab data. As lymphodepleting therapy is used in all patients with a WBC count >1000 cells/µL, febrile neutropenia is seen in patients treated with tisagenlecleucel regimen. Also, as lymphodepleting therapy is given close to the infusion of tisagenlecleucel (within two weeks), therefore, overlapping toxicities can be expected.

A therapeutic strategy for the management of febrile neutropenia is provided in Section 6.2.6.6.

2.7.1.7 Prolonged depletion of normal B cells and agammaglobulinemia

B-cell aplasia is an expected on-target toxicity of a successful CD19-directed CAR T cell therapy and a useful surrogate reflecting the persistence of CAR T cells and effectiveness of treatment. B-cell aplasia is observed in all responding patients in B-ALL. The AEs observed after tisagenlecleucel infusion were managed well by treatment with immunoglobulins.

Loss of B-cells can result in hypo- to agammaglobulinemia, potentially rendering the patients more susceptible to infections, especially with encapsulated organisms; and viral reactivation such as herpes viruses or rarely in progressive multifocal leukoencephalopathy (PML) (Section 2.7.1.7.1).

Given that a typical T-lymphocyte may have a lifespan of 40 years, tisagenlecleucel may potentially be detectable in a patient for a very prolonged period and *prolonged* depletion of B-cells may occur, in particular in the subset of patients who continue to demonstrate a tumor response. Long term data are currently not available.

2.7.1.7.1 Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy is a demyelinating disease of the central nervous system (CNS) associated with reactivation of prior John Cunningham (JC) virus infection. Patients classically present with focal neurologic deficits (e.g., weakness, speech difficulties, unsteady gait and hemiparesis), ophthalmic symptoms (e.g., homonymous hemianopia progressing to cortical blindness), personality changes, and cognitive dysfunction. Imaging (CT or MRI) shows lesions in the white matter, most commonly of the occipitoparietal lobe and without mass effect.

A therapeutic strategy for the management of B cell depletion with resulting hypogammaglobulinemia is provided in Section 6.2.6.7.

2.7.1.8 Hematopoietic cytopenias lasting greater than or equal to 28 days

Haematopoietic cytopenias are an on-target effect after tisagenlecleucel infusion and activity of tisagenlecleucel on normal B-cells.

[redacted]

Patients may exhibit haematopoietic cytopenias for several weeks as a result of exposure to tisagenlecleucel, bridging and lymphodepleting chemotherapies. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.

A therapeutic strategy for the management of hematopoietic cytopenias is provided in Section 6.2.6.8.

2.7.2 Potential safety risks

Thus far, an association with the potential safety risks briefly described below and tisagenlecleucel have not been confirmed. However, these topics are being closely monitored due to their clinical relevance.

2.7.2.1 Cerebral edema

Fatal cases of cerebral edema, soon after infusion with rapid evolution, have been reported with CAR-T cell therapies other than tisagenlecleucel; in five patients in the Rocket study evaluating JCAR015 for the treatment of ALL and in one patient in the Zuma-1 study evaluating KTE-19 for the treatment of CLL. The patient in the Zuma-1 study is described as becoming febrile on Day 1 and progressing from grade 3 to grade 4 CRS, refractory to tocilizumab and dexamethasone, by Day 4. Cerebral edema developed on Day 9, was refractory to siltuximab and mannitol, and led to death on Day 11 (Turtle et al 2017).

To date there have been no such cases reported for tisagenlecleucel.

2.7.2.2 Replication competent lentivirus (RCL) production

Replication-competent lentivirus (RCL) may be generated during tisagenlecleucel manufacturing using a lentiviral vector to encode anti-CD19 CAR or subsequently after introduction of vector transduced viable T cells into the patient.

However, an RCL resulting from manufacturing is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL Thus patients will only receive cell products that meet RCL release criteria considered sufficient to confirm the absence of RCL in tisagenlecleucel and the negligible probability of *de novo* generation of any RCL.

No AEs related to generation of RCL were noted post-infusion in the tisagenlecleucel development program. However, generation of an RCL following tisagenlecleucel infusion remains a theoretical possibility. The development of RCL could pose a risk to both the patients and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial (see [Investigational Product Handling Manual] for a description of the assays). Since the probability and characteristics of an RCL are unknown, no regulatory guideline for the management of RLC positive patients exist to date.

[redacted]

As per guidance for gene therapy medicinal products, patients exposed to tisagenlecleucel will be monitored for 15 years following last treatment for vectors persistence and RCL within the long-term follow-up study.

The Management of this potential risk is addressed in Section 6.2.6.9.

2.7.2.3 New or secondary malignancies (including vector insertion site oligo/monoclonality)

Insertion of lentiviral vector sequences throughout the genome has the potential to dysregulate local host cell gene expression with a theoretical risk of insertional oncogenesis resulting from disruption of normal function of genes that control cell growth and potential risk of development of secondary malignancies.

Vector-mediated insertional mutagenesis and subsequent malignant cell transformation after gene correction based on autologous HSC gene therapy has been observed in X-linked severe combined immunodeficiency (SCID-X1), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome (WAS), where first-generation gamma-retroviral vectors harboring long terminal repeats (LTRs) with strong enhancer/promoter sequences were used (Hacein-Bey-Abina et al 2003, Howe et al 2008, Botzug et al 2010, Stein et al 2010, Persons and Baum 2011).

In contrast, tisagenlecleucel uses third generation self-inactivating lentiviral vector. Insertional mutagenesis was addressed in two lentivirus insertion site analysis (LISA) studies where 12 batches of manufactured patient product ready for infusion and two batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration near genes of concern, no preferential sites of integration (hot spots), and no preferential outgrowth of cells harboring integration sites of concern.

Tisagenlecleucel is based on autologous, fully differentiated T cells and therefore the carcinogenicity risk is considered to be low in comparison to genetic modification or repair such as HSC. In a recent review of CAR-T cell therapies, Bonifant et al (2016) as well as Mohanlal et al (2016) discussed that to date no cases of malignant transformation have been reported for genetic modification of T cells and that there currently is no evidence for vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation. This is supported by the results of the lentivirus insertion site analysis (LISA) studies performed during the development of tisagenlecleucel.

Theoretically, CAR-positive viable T cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies (Milone et al 2009) and clinical experience to date (Porter et al 2011, Grupp et al 2013, Maude et al 2014), CAR-positive viable T cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen. In the context of tisagenlecleucel therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be either harmful depending on the extent of proliferation or beneficial, since clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials (Dudley 2002, Dudley 2005).

The management of this potential risk is addressed in Section 6.2.6.10.

[redacted]

2.7.2.4 Exacerbation of an existing or new incidence of autoimmune disease

The risk of autoimmune reaction with tisagenlecleucel is low since CD19 is not present on most normal tissue other than normal B-cells. New incidence or exacerbation of an autoimmune disorder has not been observed with tisagenlecleucel thus far. However, instances of new or exacerbation of autoimmune disorder were reported in the literature, both for diseases without an obvious underlying autoimmune cause such as stroke (Kamel and Iadecola 2012) and for ones with a clear autoimmune basis such as multiple sclerosis and optic neuritis (Feldman et al 2015). Both cellular and cytokine driven exacerbations have been observed in patients receiving chemotherapy; CNS autoimmune disorders (such as optic neuritis) have been reported to be exacerbated by both mechanisms (Skaper et al 2014, Cramer et al 2015). In addition, the use of tocilizumab, a monoclonal antibody against the IL-6 receptor, can exacerbate demyelinating disease, and therefore it is to be used with precaution in cases of demyelinating disease (Actemra® USPI). Prior chemotherapy and radiation also contribute to the risk.

No AEs associated with this potential were observed in tisagenlecleucel clinical trials.

2.7.2.5 New incidence of a hematologic disorder

There is potential risk of a hematologic disorder such as myelodysplastic syndrome, aplastic anemia or bone marrow failure, given that tisagenlecleucel is a genetically modified cell product that may have the potential to affect hematopoietic cell function, as could prior chemotherapy and radiation given for the underlying malignancy.

2.7.2.6 New incidence or exacerbation of an existing neurological event

Neurological events is an identified risk for tisagenlecleucel (see Section 2.7.1.2). Underlying neurological disorders may become exacerbated by chemotherapy, lymphodepletion or subsequent immunosuppression of tisagenlecleucel treatment. There is currently no evidence that tisagenlecleucel is associated with exacerbation of an existing neurological event.

2.7.2.7 Graft versus host disease (GVHD)

The chance of graft versus host disease (GVHD) occurring in patients is low, but it is a potential risk with tisagenlecleucel therapy in patients with mixed chimerism of host and donor hematopoietic cells due to prior allogeneic HSCT. A study of activated donor lymphocyte infusions (ex vivo activated cells collected from the donor and grown in the same fashion as tisagenlecleucel but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4) (Porter et al 2006). Of 18 ALL patients treated with autologous tisagenlecleucel therapy who had relapsed after prior allogeneic HSCT with residual mixed chimerism, none have developed GVHD after autologous tisagenlecleucel infusion (Maude et al 2014). Long term data are currently limited.

For the management of GVHD see Section 6.2.6.11.

[redacted]

2.7.3 Other risks

2.7.3.1 Pregnancy, lactation, and effects on fertility

No preclinical reproductive studies have been conducted with tisagenlecleucel to assess whether it can cause fetal harm when administered to a pregnant woman. There is a potential risk that immunologically active maternal tisagenlecleucel positive T cells may cross the placenta. The survival of normal maternal cells in the fetus is usually limited owing to effective rejection by an immunocompetent target. However maternal cells can persist in immunocompetent offspring into adult life (maternal microchimerism (MMc)). MMc has been observed in healthy fetus and adults, and was observed in up to 42% of cord blood samples from healthy newborns (Muller et al 2001). The persistence of maternal cells in offspring's tissues and circulation has been associated with autoimmune disorders. The histocompatibility antigens (HLA) disparity between mother and fetus has been hypothesized as responsible for the pathogenesis of some auto-immune diseases.

Maternal CD19 CAR T cells may be expected to cross the placental barrier and potentially exhibit MMc similar to that of normal T cells. The impact on the offspring's B cells is unknown.

The testicular environment is usually immunosuppressive to T cells, leading to control and low numbers of T lymphocytes including CD19 CART cells (Hedger and Meinhardt 2000). If transferred to female reproductive tract along with sperm, T cells are likely to be recognized as non-self by the female immune system and therefore be destroyed. A fundamental risk may arise from the presence of RCL the female organism may be exposed to after sexual intercourse. However, the principal design of the vector and the analytic measures taken during manufacturing of tisagenlecleucel will exclude the presence of RCL with highest probability, and the female risk for exposure to tisagenlecleucel and/or RCL is considered extremely low.

As it is also not known whether tisagenlecleucel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, tisagenlecleucel should not be administered to pregnant women and care should be taken to avoid conceptions.

Therefore, women of child bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, and sexually active males are excluded from clinical trials with tisagenlecleucel unless they use adequate contraception. No data are currently available to determine the duration of contraception after receiving tisagenlecleucel. Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

There is no information regarding the presence of tisagenlecleucel in human milk, the effect on the breast-fed child or the effects of tisagenlecleucel on milk production. Nursing women are excluded from participation in this study.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
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		Refer to Section 10.5.1
Not applicable	Not applicable	
Other Secondary		Refer to Section 10.5.2
Evaluate the efficacy of tisagenlecleucel as measured by additional efficacy measures, including ORR, DOR, PFS and OS	ORR, including complete response (CR) and partial response (PR) determined by IRC in the FAS based on Lugano 2014 classification. DOR, defined as time from achievement of CR or PR to relapse 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	Levels of pre-existing and treatment induced immunogenicity Cellular kinetic parameters (Cmax, AUCs, Tlast), concentration-time profile tisagenlecleucel by immunogenicity category (positive/negative)	

[redacted]

Objective	Endpoint	Analysis
and humoral) on cellular kinetics, efficacy and safety	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	

[redacted]

Objective	Endpoint	Analysis
[redacted]		

4 Study design

4.1 Description of study design

This single arm, multi-center, 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, and Treatment and Follow-up (Section 7.1). Treatment and Follow-up Phase will include infusion and safety and efficacy follow-up for 24 months (Table 7-1). For all patients who received a tisagenlecleucel infusion, additional survival follow-up will be made to determine survival status every 3 months, survival status can also be obtained via phone contact if the quarterly schedule does not align with a scheduled visit.

Efficacy will be evaluated using PET/CT/MRI based on Lugano classification (Cheson et al 2014) response criteria (see Appendix 14.1). If local health authorities require the use of specific imaging modalities (e.g., MRI) and/or a different imaging schedule for disease response assessment purposes a decision will be made on a case by case basis upon discussion between Novartis and the Investigator. Imaging will be performed at Months 3, 6, 9, 12, 18, 24 months, and every 6 months (Q6M) 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.

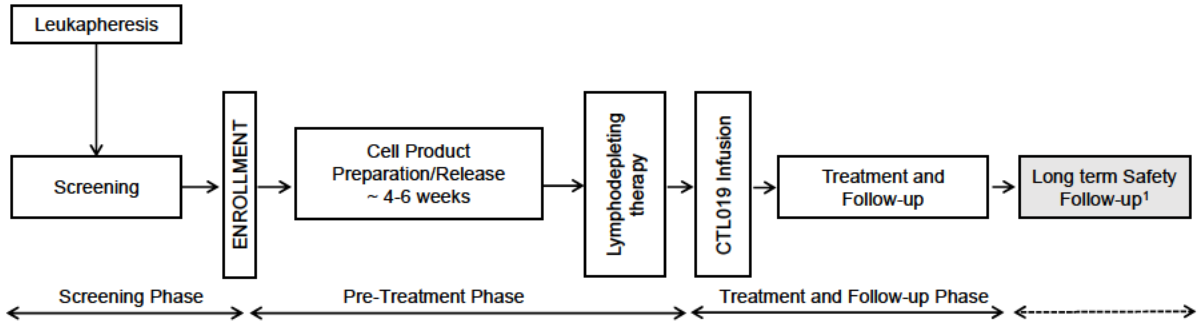
A staggered approach will be utilized at each new study site (with no prior experience administering CAR T cell therapies) and will occur as follows:

- 1st patient infusion, wait 14 days
- 2nd patient infusion, wait 14 days
- 3rd patient infusion

Following completion of this staggered infusion of the first three patients, the site may infuse subsequent patients without staggering.

Safety will be assessed throughout the study.

Figure 4-1 Study design



1. Long term safety follow-up as per health authority guidance conducted under a separate LTFU protocol (CTL019A2205B).

[redacted]

4.2 Timing of interim analyses and design adaptations

One interim analysis is planned for the study 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.

Please refer to Section 10.7.

4.3 Definition of end of study

The end of study is when all patients have completed Month 24 evaluation or discontinued prematurely. Patients who have completed their Month 24 visit before the end of the study will be followed for assessments at onsite visits every 6 months (Q6M) until the end of the study.

The primary analysis will be performed when 90 patients have received tisagenlecleucel infusion and completed 6 months from study Day 1 infusion or discontinued earlier.

In addition, semiannual and annual evaluations will be performed for up to 15 years from the date of infusion on all patients under a separate long term follow-up (LTFU) protocol as recommended by Health Authority guidance for patients treated with gene therapies. All patients who either complete or prematurely discontinue from the study will be enrolled in this destination protocol at the time of study completion/discontinuation (a separate informed consent form will be provided for this protocol; Section 7.1.8).

Patients may continue to be followed under the current protocol for survival, which can be conducted via a form or telephone contact until the end of the study as defined above and then under the LTFU protocol [CCTL019A2205B].

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should this be necessary, the patient must be seen as soon as possible and the same assessments should be performed as described in Section 7.1.6 for a withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. For patients who have received tisagenlecleucel infusion, a long term post-study follow-up for delayed AEs including monitoring for lentiviral safety will still continue under a separate destination protocol (CCTL019A2205B) for 15 years post infusion per health authority guidelines. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

[redacted]

5 Population

5.1 Patient population

Approximately 113 adult patients with r/r FL will be enrolled (for r/r/ FL definition see Inclusion Criterion 4) to obtain 90 patients treated with tisagenlecleucel. Patients enrolled in this study are not permitted to participate in additional investigational drug or device studies simultaneously. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

It is anticipated that the life expectancy of enrolled patients is 12 weeks or more.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Written informed consent prior to any screening procedures
2. ≥18 years of age at the time of ICF signature
3. FL (Grade 1, 2, 3A) confirmed histologically by central pathology review before tisagenlecleucel infusion.

   Sufficient formalin-fixed paraffin-embedded (FFPE) tumor samples obtained for this study with a corresponding pathology report must be submitted. If not clinically feasible, an archival tumor biopsy from the most recent relapse may be submitted. However, in case of clinical symptoms, abnormal laboratory tests, and radiological images suggesting histologic transformation, a fresh biopsy will be required. Excisional biopsies should be submitted; if not possible, a core needle biopsy is allowed. Fine needle aspiration (FNA) is not allowed.
4. FL meeting one of the following criteria:
   - Refractory to a second line or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second line or later line of systemic therapy
   - Relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion
   - Relapsed after autologous HSCT

   NOTE: Previous treatment with other FL-targeting medications (e.g. PI3K inhibitors) is allowed provided that patients recovered from all treatment-related adverse events.
5. Radiographically measurable disease at screening defined as:
   - At least one nodal lesion greater than 20 mm in the long axis, regardless of the length of the short axis AND/OR
   - Extranodal lesions (outside lymph node or nodal mass, including liver and spleen) greater than 10 mm in long AND short axis

   For detailed information please refer to Appendix 1 Guidelines for efficacy evaluation in lymphoma studies
6. ECOG performance status that is either 0 or 1 at screening
7. Patients must meet the following laboratory values without transfusion at screening:
   - Absolute neutrophil count (ANC) ≥ 1,000/mm^3 (≥ 1×10^9/L)

[redacted]

- Absolute lymphocyte count (ALC) > 300/mm^3 (> 0.3×10^9/L)
- Absolute number of CD3+ T cells > 150/mm^3 (> 0.15×10^9/L)
- Platelets ≥ 50 000/mm^3 (≥ 50×10^9/L)
- Hemoglobin ≥ 8.0 g/dl (≥ 4.9 mmol/L)
- A serum creatinine of ≤1.5 times ULN or eGFR ≥ 60 mL/min/1.73 m^2
- ALT/AST ≤ 5 times the ULN
- Total bilirubin ≤ 1.5 times ULN (with the exception of patients with Gilbert's syndrome. Patients with Gilbert's syndrome may be included if their total bilirubin is ≤ 3.0 times ULN and direct bilirubin ≤ 1.5 times ULN

8. Adequate pulmonary function defined as:
    - No or mild dyspnea (≤ Grade 1)
    - Oxygen saturation measured by pulse oximetry > 90% on room air
9. Must have a leukapheresis product of non-mobilized cells accepted for manufacturing

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Evidence of histologic transformation
2. Follicular Lymphoma Grade 3B
3. Prior anti-CD19 therapy
4. Prior gene therapy
5. Prior adoptive T cell therapy
6. Prior allogeneic hematopoietic stem cell transplant
7. Active CNS involvement by malignancy
8. Active neurological autoimmune or inflammatory disorders (e.g. Guillain-Barre syndrome, Amyotrophic Lateral Sclerosis)
9. Investigational medicinal product within the last 30 days or five half-lives (whichever is longer) prior to screening

    NOTE**:** Investigational therapies must not be used at any time while on study until the first progression following tisagenlecleucel infusion
10. Presence of active or prior hepatitis B or C as indicated by serology (for detailed criteria see Appendix 2) Serology must be repeated, if the interval between testing prior to lymphodepletion and tisagenlecleucel infusion exceeds 8 weeks
11. Presence of HIV antibody. Serology must be repeated, if the interval between testing prior to lymphodepletion and tisagenlecleucel infusion exceeds 8 weeks
12. Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to tisagenlecleucel infusion)
13. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment

[redacted]

- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
- LVEF <45% as determined by ECHO or MRA or MUGA
- NYHA functional class III or IV (Chavey et al 2001)

14. Previous or concurrent malignancy with the following exceptions:
    a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to enrollment)
    b. *In situ* carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to enrollment
    c. A primary malignancy which has been completely resected and in complete remission for ≥ 3 years at the time of enrollment
15. Pregnant or nursing (lactating) women

    NOTE: female study participants of reproductive potential must have a negative serum or urine pregnancy test performed within 24 hours before leukapheresis, lymphodepletion and prior to tisagenlecleucel infusion.
16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[redacted]

NOTE: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

17. Sexually active males must use a condom during intercourse while taking study treatment and for at least12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.
18. Intolerance to the excipients of the tisagenlecleucel cell product.

6 Treatment

6.1 Study treatment

Tisagenlecleucel is an autologous cellular immunotherapy product that is comprised of CD3+ T cells that have undergone *ex vivo* T cell activation, gene modification, expansion and formulation in infusible cryomedia. The transgene to be expressed via lentiviral vector transduction is a CAR targeted against the CD19 antigen. The CAR contains a murine scFv that targets CD19 linked to a transmembrane region derived from the CD8 receptor, which is linked to an intracellular bipartite signaling chain of TCR-ζ (or CD3-ζ) and 4-1BB intracellular signaling domains. The extracellular scFv with specificity for CD19 is derived from a mouse monoclonal antibody. T cells which are enriched from a patient leukapheresis unit are expanded *ex vivo* using commercially available magnetic beads that are coated with anti-CD3 and anti-CD28 monoclonal antibodies. The cells are transduced with the CD19 CAR lentiviral vector which ensures that only peripheral white blood cells enriched for lymphocytes are exposed to the vector. The residual non-integrated vector is washed away during the process. Tisagenlecleucel cells will be expanded *ex vivo* for up to 10 days. At the end of the culture, the tisagenlecleucel cells are depleted of magnetic beads, washed, concentrated, and cryopreserved**.** Results from a release testing procedure are required prior to release of the product for infusion.

6.1.1 Dosing regimen

The recommended dose will consist of a single intravenous (i.v.) infusion of 0.6 – 6.0 x 10^8 CAR-positive viable T cells.

6.1.2 Bridging therapy

As it is not expected that the patients will progress rapidly during the screening and pre—treatment period, the patients are unlikely to need bridging therapy. If, however, a bridging therapy is administered, the investigator should follow the recommendations described in Section 6.4.1 Prohibited concomitant therapy.

PET-CT should be performed after bridging and prior to tisagenlecleucel infusion unless the bridging therapy consists of steroids only. Patients with no measurable disease at baseline after bridging therapy will still receive tisagenlecleucel infusion.

[redacted]

6.1.3 Lymphodepleting chemotherapy

It is anticipated that many patients will have been receiving chemotherapy for relapsed or resistant disease. Prior to tisagenlecleucel infusion, each patient should receive lymphodepleting chemotherapy. This may be omitted in case of significant cytopenia (e.g. WBC <1,000 cells/µL, absolute lymphocyte count <200/µL) or any condition that, in the investigator's opinion, precludes lymphodepleting chemotherapy.

When given, lymphodepleting chemotherapy should be started 1 week before tisagenlecleucel infusion so that the tisagenlecleucel cells will be given 2 to 6 days after completion of the lymphodepleting chemotherapy. The chemotherapy start date will vary based on the selected chemotherapy. The purpose of this chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of tisagenlecleucel cells. For lymphodepleting chemotherapy, cyclophosphamide-based regimens are preferred agents as there is the most experience with the use of these agents in facilitating adoptive immunotherapy. The first option as lymphodepleting regimen is:

- Fludarabine (25 mg/m^2 intravenously [i.v.] daily for 3 doses) and cyclophosphamide (250 mg/m^2 i.v. daily for 3 doses starting with the first dose of fludarabine)

Note: Side effects of fludarabine can include severe nervous system events of seizure, agitation, blindness, coma and death. Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have been reported to occur after one or more cycles of treatment with fludarabine phosphate injection. It may also severely decrease bone marrow function (Fludarabine full prescribing information). Cyclophosphamide toxicities include cardiac dysfunction. Acute cardiac toxicity has been reported with doses as low as 2.4 g/m^2 to as high as 26 g/m^2, usually as a portion of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures. In a few instances with high doses of Cyclophosphamide, severe, and sometimes fatal, congestive heart failure has occurred after the first Cyclophosphamide dose. Severe marrow suppression is seen and occasional anaphylactic reactions have been reported. Hemorrhagic cystitis, pulmonary toxicity (pneumonitis, pulmonary fibrosis and pulmonary veno-occlusive disease leading to respiratory failure) and veno-occlusive liver disease may occur (Cyclophosphamide full prescribing information).

If there was previous grade IV hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated resistance to a previous cyclophosphamide-containing regimen, then the following regimen should be used:

- Bendamustine 90 mg/m^2 i.v. daily for 2 days

Note: Side effects of bendamustine include severely decreased bone marrow function, nausea, vomiting and diarrhea; jaundice may occur, including without other signs of hepatic dysfunction. Fatal and serious cases of liver injury have been reported (Bendamustine full prescribing information).

No other regimen is allowed for lymphodepletion.

Female patients of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the start of lymphodepleting therapy. If the patient does not require

[redacted]

lymphodepleting therapy, she should still have a negative pregnancy test at the required visit that takes place within 24 hours prior to tisagenlecleucel infusion.

6.1.4 Tisagenlecleucel infusion

Manufacturing of the tisagenlecleucel cell product will start once a leukapheresis product has been accepted by the Novartis designated manufacturing facility and the patient has been enrolled. The 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. For details on the cryopreserved components, and the specific storage and handling requirements of the tisagenlecleucel cell product, see the [Investigational Product Handling Manual].

6.1.4.1 Pre-Infusion Evaluation

If any of the following criteria is met tisagenlecleucel infusion must be delayed until resolution to grade 1. If the period of delay is more than 4 weeks from completing lymphodepletion and there is no significant cytopenia (see Section 6.1.3) lymphodepletion should be repeated, and these criteria will need to be re-checked prior to tisagenlecleucel infusion.

1. Rapidly progressing primary disease
2. Clinical evidence of CNS involvement by primary disease
3. Laboratory abnormalities that, in the opinion of the investigator, may impact patient safety or the patient's ability to receive tisagenlecleucel.
4. Following clinical abnormalities:
   - Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 90% or presence of progressive radiographic abnormalities on chest x-ray
   - Cardiac arrhythmia not controlled with medical management
   - Hypotension requiring vasopressor support
   - Active infection, as evidenced by positive blood cultures for bacteria, fungi, or PCR positivity for viral DNA in blood within 72 hours of tisagenlecleucel cell infusion, or clinical or radiographic evidence
5. A significant change in clinical status that would, in the opinion of the investigator, increase the risk of adverse events associated with tisagenlecleucel
6. Concomitant medications as described in Section 6.4.1
7. Positive influenza test within 10 days prior to tisagenlecleucel infusion (please refer to Table 7-1). If the patient is positive for influenza, oseltamivir phosphate or zanamivir should administered for 10 days as preventative treatment (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their 10 day preventative treatment course **prior** to receiving tisagenlecleucel. The test does not need to be repeated prior to tisagenlecleucel infusion however if flu-like or respiratory signs and symptoms are present, tisagenlecleucel infusion should be delayed until the patient is asymptomatic. For patients residing in the United States, Canada, Europe and Japan, influenza testing is required during the months of October through May (inclusive). For patients residing in the southern hemisphere such as Australia, influenza testing is required during the months of April

[redacted]

through November (inclusive). For patients with significant international travel, both calendar intervals above may need to be considered.

8. Live vaccines must not be used in tisagenlecleucel recipients for at least 2 weeks prior to the start of lymphodepleting chemotherapy, during tisagenlecleucel treatment, and until immune recovery following treatment with tisagenlecleucel.

6.1.4.2 Additional safety procedures prior to administration

Tumor Lysis Syndrome

The risk of tumor lysis syndrome (TLS) is dependent on disease burden. Patients will be closely monitored both before and after lymphodepleting chemotherapy and tisagenlecleucel infusion including blood tests for potassium and uric acid. Patients with elevated uric acid or high tumor burden will receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat). Infection prophylaxis should follow local guidelines dictated only by the preceding lymphodepleting chemotherapy. Infection prophylaxis *per se* for tisagenlecleucel is not recommended.

Infections

Infection prophylaxis with regard to lymphodepletion and other additional treatments should follow local guideline. Infection prophylaxis is not recommended in the setting of tisagenlecleucel infusion.

Cytokine Release Syndrome

Prior to tisagenlecleucel infusion two doses of tocilizumab per patient (for the first 3 weeks after tisagenlecleucel infusion) must be confirmed as available and must be available for infusion within 2 hours for the management of CRS related adverse events (see Section 6.2.6.1 for details).

Premedication

Side effects from T cell infusion can include fever, chills and/or nausea. All patients should be pre-medicated with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved with acetaminophen (paracetamol). Steroids should NOT be used for premedication. It is recommended that patients NOT receive systemic corticosteroids other than physiologic replacement, except for serious emergency, since this may have an adverse effect on tisagenlecleucel cell expansion and function.

Supportive care

Local guidelines will be followed for the supportive care of immunosuppressed and chemotherapy treated patients. All blood products administered should be irradiated. For details about prohibited concomitant medications and non-drug therapies please refer to Section 6.4.1.

[redacted]

6.1.4.3 Cell thawing and infusion of tisagenlecleucel product

Coordination of the timing of thaw of tisagenlecleucel product and infusion will be done. For detailed instructions on the storage, handling, preparation and administration of the tisagenlecleucel cell product, refer to the [Investigational Product Handling Manual].

Vital signs (temperature, respiration rate, pulse, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion and then approximately every 15 minutes for one hour and then every hour for the next two hours, or until these signs are satisfactory and stable.

A study investigator MUST evaluate the patient just prior to infusion to ensure the patients meets tisagenlecleucel infusion criteria. Trained study staff will administer the tisagenlecleucel infusion using precautions for immunosuppressed patients. Protective isolation should follow institutional standards and policies. Emergency medical equipment should be available during the infusion in case the patient has a significant reaction to the infusion such as anaphylaxis or severe hypotension. After cell thawing, tisagenlecleucel cell product should **NOT** be washed prior to infusion, and all contents will be infused. A single dose of 0.6 to 6 x 10^8 CAR-positive viable T cells will be administered via intravenous infusion, preferably through a central line.

Following tisagenlecleucel infusion, should emergency treatment be required in the event of life-threatening hypersensitivity or other acute infusion-related reaction, supportive therapy such as oxygen, bronchodilators, epinephrine, antihistamines, and corticosteroids should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

6.1.5 Treatment duration

A single dose of tisagenlecleucel will be administered.

6.2 Dose escalation guidelines

Not applicable

6.2.1 Starting dose rationale

Not applicable

6.2.2 Provisional dose levels

Not applicable

6.2.3 Guidelines for dose escalation and determination of (MTD/RP2D/RDE)

Not applicable

6.2.4 Definitions of dose limiting toxicities (DLTs) in a phase II study

Not Applicable

[redacted]

6.2.5 Toxicity management, stopping rules and study termination

It is expected that AEs will occur frequently in this population based on the underlying advanced malignancy and that these can be SAEs. Therefore, there is no specific occurrence of SAEs that define a stopping rule, but the review of SAEs will form the basis for potential early stopping of the study. The review of these adverse events, and any decision to prematurely stop patient enrollment, will be determined by the Steering Committee (SC) and reviewed by the IRB.

Premature termination of the clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB, the SC, or determination that there are problems in the cell product generation or safety at the discretion of the study investigators. Additionally, recruitment may be stopped at the sponsor's discretion and may include reasons such as low recruitment, protocol violations, or inadequate data recording.

6.2.6 General toxicity management considerations

Patients infused with tisagenlecleucel are at risk of developing a number of AE that are related either to tisagenlecleucel itself, other therapies (e.g. immunochemotherapy) and conditions concurrent with the patient's primary disease. Following tisagenlecleucel infusion, patients can be discharged from the treating site only if, in the investigator's opinion, they do not demonstrate any adverse events or worsening of underlying diseases. This chapter describes the management of such AEs.

Drug and non-drug therapies used to treat AEs must be recorded on appropriate CRFs.

6.2.6.1 Cytokine Release Syndrome (CRS)

Ensure that tocilizumab is available on site prior to infusion of tisagenlecleucel. Supportive care, tocilizumab, and corticosteroids have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most patients.

Identify cytokine release syndrome (CRS) based on clinical presentation (see Section 2.7.1.1). Evaluate for and treat other causes of fever, hypoxia, and hypotension. Although signs and symptoms of CRS occur in most cases within 1-14 days after tisagenlecleucel infusion, monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with tisagenlecleucel. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated.

A detailed treatment algorithm for the management of CRS (Lee at al 2014) is presented below in Table 6-1 and Table 6-2. Patients will be required to remain proximal to the treating site for the first 4 weeks.

[redacted]

Table 6-1 CRS management

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Grade 1 Mild general symptoms requiring symptomatic treatment only e.g. fever, nausea, fatigue, headache, myalgia, etc.	After excluding other causes (e.g. infection), treat specific symptoms with e.g. antipyretics, anti-emetics, anti-analgesics, etc.	Not applicable	Not applicable
Grade 2 Symptoms requiring moderate intervention: Hypoxia requiring low-flow oxygen supplementation (<40%) or Hypotension requiring intravenous fluids and low dose of one vasopressor or Grade 2 organ toxicities	Oxygen supplementation Start intravenous fluids and, if no improvement, follow with a low-dose vasopressor Treat organ toxicities as per local guidelines	8 mg/kg intravenously (maximum 800 mg) over 1 hour. Repeat every 8 hours, if not responsive to intravenous fluids and increasing oxygen supplementation. Limit to 3 doses within 24 hours: maximum total of 4 doses.	If no improvement after 24 hours of treatment with tocilizumab, administer 1 mg/kg methylprednisolone intravenously twice daily (2 mg/kg as initial bolus can be given) or equivalent steroid dose. Continue until Grade 1 or less, then taper over 3 days.
Grade 3 Symptoms requiring aggressive intervention: Hypoxia requiring high-flow oxygen supplementation (≥40%) or Hypotension requiring high-dose* or multiple vasopressors or Grade 3 organ toxicities or Grade 4 transaminitis	Oxygen supplementation Intravenous fluids and high-dose* vasopressor/s Treat organ toxicities as per local guidelines	See Grade 2	See Grade 2
Grade 4 Life-threatening symptoms requiring ventilator support, etc. or Grade 4 organ toxicity (excluding transaminitis)	Oxygen supplementation incl. ventilator support Intravenous fluids and high-dose* vasopressor/s Treat organ toxicities as per local guidelines	See Grade 2	Administer methylprednisolone 1000 mg intravenously daily (or equivalent steroid dose) for 3 days. If improves, then manage as per Grade 2.

*See Table 6-2

[redacted]

Table 6-2 High-dose vasopressors

Vasopressor	Dose to be given for ≥ 3 hours
Norepinephrine monotherapy	≥ 20 mcg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200 mcg/min
Epinephrine monotherapy	≥ 10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 10 mcg/min*
If on combination vasopressors (not vasopressin)	NE of ≥ 20 mcg/min*

*Vasopressin and Septic Shock Trial (VASST) Norepinephrine Equivalent Equation:
NE dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10] (Russell et al 2008)

Other anti-cytokine therapies may also be considered upon their availability, if the patient does not respond to tocilizumab. If the patient experiences ongoing CRS despite administration of anti-cytokine directed therapies, anti-T cell therapies such as cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab may be considered. These therapies need to be captured in appropriate CRFs.

The management of CRS is based solely upon clinical parameters as described in Section 2.7.1.1. Ferritin, CRP and serum cytokine levels should NOT be used for clinical management decisions. Cases of transient left ventricular dysfunction, as assessed by ECHO, have been reported in some patients with severe (Grade 4) CRS. Therefore consideration should be given to monitoring cardiac function by ECHO during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

6.2.6.2 Neurological adverse events during CRS

Patients should be monitored for neurological events following tisagenlecleucel infusion, in particular during and after resolution of CRS. Prompt and effective management of CRS may prevent some neurological complications associated with tisagenlecleucel therapy. Supportive treatment should be given for tisagenlecleucel associated neurological events as per standard of care and diagnostic work-up considered to exclude other causes for these symptoms.

6.2.6.3 Hypersensitivity including acute infusion reactions

Patients should be monitored for signs and symptoms of hypersensitivity following initiation of tisagenlecleucel infusion and treated appropriately. Tisagenlecleucel is contraindicated in patients with known hypersensitivity to tisagenlecleucel or to any component of the product formulation.

As appropriate, prophylactic medications should be administered to minimize the risk of immediate hypersensitivity including acute infusion reactions. It is recommended to pre-medicate all patients with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine within approximately 30-60 minutes prior to tisagenlecleucel infusion. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed for fever not responding to acetaminophen. Steroids should not be used for premedication. Systemic corticosteroids should only be used for severe conditions.

[redacted]

Should emergency treatment be required in the event of life-threatening hypersensitivity or other infusion-related reaction, supportive therapy such as oxygen and drug treatment should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

6.2.6.4 Tumor Lysis Syndrome (TLS)

Patients should be closely monitored for signs and symptoms of TLS both before and after lymphodepleting chemotherapy and tisagenlecleucel infusion including relevant laboratory tests. To minimize risk of TLS, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to tisagenlecleucel infusion. Events should be managed according to local guidelines.

Depending on the study phase, the following measures should be followed:

- Screening phase:
  - Prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat), and increased oral/ i.v. hydration prior to lymphodepleting chemotherapy and tisagenlecleucel infusion should be given in patients with elevated uric acid or high tumor burden
  - Prompt supportive care in case of acute TLS (i.v. fluids and rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)
- Post-infusion monitoring phase:
  - Frequent monitoring of the following laboratory tests (2 to 3 times/week for 3 weeks from start of lymphodepleting chemotherapy, then weekly): potassium, phosphorus, calcium, creatinine, and uric acid
  - Encourage oral hydration

Based on laboratory and clinical TLS criteria (modified from Cairo and Bishop (2004)), the following measures for TLS should be also followed:

Laboratory TLS

Laboratory TLS is defined as two or more of the following values within three days before or in the days following tisagenlecleucel infusion:

- Uric acid ≥ 8 mg/dL or 25% increase from baseline
- Potassium ≥ 6 mEq/L or 25% increase from baseline
- Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline
- Calcium ≤ 7 mg/dL or 25% decrease from baseline

Regimen:

If none or one of the laboratory values above is abnormal, continue to manage with allopurinol or a non-allopurinol alternative (e.g. febuxostat) and oral fluids. If uric acid remains elevated, consider i.v. fluids, rasburicase, and hospital monitoring.

Laboratory TLS should be managed with i.v. fluids, laboratory blood tests every 6 to 8 hours and inpatient care. Cardiac monitoring and rasburicase should be considered if uric acid remain elevated

[redacted]

Clinical TLS

- Defined as the presence of laboratory TLS and ≥ 1 of the following criteria that cannot be explained by other causes:
- Serum creatinine ≥ 1.5 times the upper limit of the age-adjusted normal range
- Symptomatic hypocalcemia
- Cardiac arrhythmia

Clinical TLS should be managed with i.v. fluids, laboratory blood tests every 6 to 8 hours, cardiac monitoring, rasburicase/allopurinol/febuxostat and inpatient care (consider ICU).

6.2.6.5 Infections

Patients with active, uncontrolled infection should not start tisagenlecleucel treatment until the infection is resolved.

Patients should be monitored for signs and symptoms of infection and treated appropriately. As appropriate, prophylactic antibiotics should be administered and surveillance testing prior to and during treatment with tisagenlecleucel should be employed.

Institutional guidelines for vaccination (e.g. pneumococcus) should be followed before starting tisagenlecleucel therapy. As the lack of effective B cells after infusion makes the likelihood of a systemic infection considerable, vaccination with live virus vaccines should not be given for at least 2 weeks prior to the start of lymphodepleting chemotherapy, during tisagenlecleucel and until immune recovery following treatment with tisagenlecleucel.

Any suspected cases of viral hepatitis or HIV should be referred to a specialist.

In patients with low immunoglobulin levels preventive measures such as immunoglobulin replacement and rapid attention to signs and symptoms of infection should be implemented as per age and local specific guidelines.

6.2.6.6 Febrile neutropenia

Febrile neutropenia (significantly decreased neutrophil count with fever) may develop in the course of chemotherapy (including lymphodepletion) and may be concurrent with CRS. A febrile patient should be evaluated for infection (Section 2.7.1.5) and CRS (Section 2.7.1.1) and managed appropriately with fluids, antibiotics, and supportive care, if applicable.

In the event that the patient develops sepsis or systemic bacteremia following tisagenlecleucel cell infusion, appropriate cultures and medical management should be initiated. If a contaminated tisagenlecleucel cell product is suspected, the product can be retested for sterility using archived samples that are stored at the manufacturing site.

6.2.6.7 B cell depletion and/ or hypogammaglobulinemia

Monitor immunoglobulin levels after treatment with tisagenlecleucel, use infection precautions including antibiotic prophylaxis and immunoglobulin replacement as appropriate and per local standard of care.

In case of new or worsening symptoms suggestive of PML, consultation with a neurologist should be considered

[redacted]

6.2.6.8 Hematopoietic cytopenias lasting greater than or equal to 28 days

Myeloid growth factors are not recommended until CRS has been resolved and typically not until 28 days following tisagenlecleucel infusion. Haematopoietic cytopenias should be managed with standard measures of observation, blood product support growth factors and/or antibiotics as indicated and per local standard of care.

6.2.6.9 Replication competent lentivirus (RCL) production

If a positive RCL assay result is obtained from a patient blood specimen, (e.g., as detected by Vesicular Stomatitis Virus/Glycoprotein (VSV-G) quantitative PCR), the Investigator will be informed and the patient rescheduled for a retest of the DNA test. The patient must be isolated until an understanding of how to manage the patient becomes clear. Some considerations are:

- Intensive follow-up of the patient in consultation with gene therapy experts, study investigators, and Health Authorities
- Inform local and country specific public health officials
- Identify sexual partners and provide appropriate counseling and intervention

6.2.6.10 New or secondary malignancies including vector insertion site oligo/monoclonality)

If uncontrolled T cell proliferation occurs (e.g. expansion of T cells in the absence of CD19 antigen), patients may be treated with corticosteroids such as methylprednisolone (2 mg/kg/d i.v.) or chemotherapy, such as high dose cyclophosphamide. Investigators should further discuss this with the sponsor. Toxicity associated with allogeneic or autologous T cell infusions has been managed with a course of pharmacologic immunosuppression. T cell associated toxicity has been reported to respond to systemic corticosteroids (Lamers et al 2006).

This theoretical toxicity is distinct from the toxicity associated with a CRS that develops during T cell proliferation upon exposure to CD19 expressing cells. CRS associated with T cell expansion is managed with anti-cytokine therapy, not immunosuppressants, and is addressed in Section 6.2.6.1.

Follow up of secondary malignancy

For patients treated with tisagenlecleucel, treating physician/ healthcare providers should contact Novartis if the patient develops a secondary malignancy. Upon clinical confirmation of a secondary malignancy, blood samples should be collected for cellular kinetic analysis by qPCR and flow cytometry. Two tubes of blood are requested: 10 ml sample of PBMCs in a sodium heparin collection tube and 6 ml of blood in EDTA tube. [redacted]. Additional details for sample handling and shipping are outlined in the laboratory manual.

6.2.6.11 Graft versus host disease (GVHD)

GVHD can be severe but can be controlled with steroids and other immunosuppressants as per local standard of care.

[redacted]

6.2.7 Criteria for discontinuing a patient's participation in the study

If a patient develops a condition that precludes tisagenlecleucel infusion after enrollment but before infusion, the patient will be prematurely discontinued. This will be done at the judgment of the PI, and could include for example, the occurrence of an intercurrent illness requiring the institution of systemic immunosuppression.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

Not applicable

6.3.2 Additional safety monitoring and follow-up for toxicities

6.3.2.1 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of tisagenlecleucel, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as non-serious AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 14.4.1 in Appendix 4 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 14.4.1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 14.4.1. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate. If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

- Discontinuation of the investigational drug (refer to Section 7.1.5), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event, which can include based on investigator's discretion:
    - Serology tests, imaging (e.g., such as abdominal US, CT or MRI, as appropriate) and pathology assessments, gastroenterologist's or hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of

[redacted]

concomitant drug use, exclusion of underlying liver disease, obtaining a history of exposure to environmental chemical agents.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

6.3.2.2 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN

For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically

[redacted]

significant", thus, met the definition of SAE and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.2.3 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR new onset dipstick proteinuria ≥ 3+ OR new onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

Every renal laboratory trigger or renal event as defined in Appendix 5, Section 14.5 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 5.

6.4 Concomitant therapy

Clinically significant prescription and nonprescription medication, excluding vitamins, and herbal and nutritional supplements, and procedure-related (inpatient or outpatient) medications taken by the patient during the 30 days prior to screening will be recorded. At every visit following the screening visit up to the end of the study, concomitant medications will be recorded in the medical record and on the appropriate CRF. During selected trial phases, concomitant medication collection will be modified as outlined in Appendix 3: Tisagenlecleucel Modified Data Reporting- Treatment and Follow-Up Phase, CRF Completion Guidelines (CCGs). Modified collection of concomitant medication information during these periods is designed to capture tisagenlecleucel-related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented.

The following guidelines must be adhered to during the study:

- Granulocyte macrophage-colony stimulating factor (GM-CSF) should be avoided due to the potential to worsen CRS symptoms. Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of tisagenlecleucel infusion and long acting G-CSF should not be given within 10 days of tisagenlecleucel infusion. The effects of granulocyte colony stimulating factor (G-CSF) on the other hand, are unknown.
- Steroids or other immunosuppressant drugs should NOT be used as pre-medication for tisagenlecleucel therapy (refer to Section 6.1.4.1) or following tisagenlecleucel infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances. Use of steroids with blood product administration should be eliminated just prior to and following tisagenlecleucel if possible or at least minimized.
- Patients with moderate to severe signs and symptoms attributable to CRS should be managed with supportive care and administration of tocilizumab as defined in Table 6-2 and Section 6.2.6.1.

[redacted]

- The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study.

6.4.1 Prohibited concomitant therapy

The patient must be told to notify the investigational site about any medications he/she takes. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the appropriate CRFs.

Medication restrictions prior to leukapheresis

For medication restrictions before leukapheresis, please refer to the recent [Investigational Leukapheresis, Cryopreservation and Scheduling Manual].

Medication restrictions prior to tisagenlecleucel infusion

1. **Steroids:** Therapeutic doses of steroids must be stopped > 72 hours or 5 half-lives, whichever is greater, prior to tisagenlecleucel infusion. However, the following physiological replacement doses of steroids are allowed: ≤ 40 mg/day hydrocortisone or equivalent
2. **Steroids or other immunosuppressant drugs** should NOT be used as pre-medication for tisagenlecleucel therapy (refer to Section 6.1.4.1/ Pre-Infusion Evaluation) or following tisagenlecleucel infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances. Use of steroids with blood product administration should be avoided just prior to and following tisagenlecleucel if possible or at least minimized.
3. **Antibody use** including anti-CD20 therapy (e.g., rituximab) should not be used within 4 weeks prior to tisagenlecleucel infusion
4. **CNS disease prophylaxis or intrathecal therapy** must be stopped > 1 week prior to tisagenlecleucel infusion (e.g. intrathecal methotrexate)
5. **Radiation therapy** must be stopped >2 weeks prior to tisagenlecleucel infusion
6. **Investigational therapies** must not be used at any time while on study until the first progression following tisagenlecleucel infusion
7. **Live vaccines** must not be used in tisagenlecleucel recipients for at least 2 weeks prior to lymphodepletion and during tisagenlecleucel treatment until immune recovery
8. **Granulocyte macrophage-colony stimulating factor (GM-CSF)** should be avoided due to its potential to worsen CRS symptoms. Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of tisagenlecleucel infusion and long acting G-CSF should not be given within 10 days of tisagenlecleucel infusion.
9. **Antiproliferative therapies,** other than lymphodepletion including low dose daily or weekly maintenance chemotherapy) should not be used within 2 weeks of leukapheresis and 2 weeks prior to infusion.
10. Short acting drugs used to treat primary disease (e.g. hydroxyurea, tyrosine kinase inhibitors) must be stopped > 72 hour prior to leukapheresis and > 72 hours prior to tisagenlecleucel

[redacted]

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Clinical Data Management System interface.

The investigator or designated staff will contact the IRT system and provide the requested identifying information for the patient to register them into the IRT system. Once assigned, the Subject No. must not be reused for any other subject. If the patient fails to be enrolled or to start treatment for any reason, the reason will be entered into the appropriate CRF page. The IRT system must be notified within 2 days that the patient was not treated.

6.5.2 Treatment assignment or randomization

This is a single-arm open-label study. Patients will be enrolled and assigned to treatment upon confirmation of all clinical eligibility criteria by the investigator, and acceptance of the leukapheresis product for manufacturing.

6.5.3 Treatment blinding

This is a single-arm open-label study.

6.6 Tisagenlecleucel preparation and dispensation

For details on the cryopreserved components, and the specific storage and handling requirements of the tisagenlecleucel product, see the [Investigational Leukapheresis, Cryopreservation & Scheduling Manual and Investigational Product Handling Manual].

6.6.1 Tisagenlecleucel packaging and labeling

The tisagenlecleucel product will be shipped from Novartis in a dry vapor shipper where temperature is maintained and continuously monitored. Confirmation of temperature excursions during transport and unloading of the tisagenlecleucel product and accompanying documentation will be done. The tisagenlecleucel product will be carefully examined to ensure that it is intact and free from damage. The tisagenlecleucel product will be transferred to on-site storage.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

Each infusion bag will typically contain 10 mL-50 mL of cells. Higher volumes may occasionally be necessary depending on transduction efficiency to formulate the recommended dose of 6 x 10^8 viable transduced T cells.

[redacted]

Each infusion bag will have affixed to it a label containing the following: A product identifier, the proper name of the product, and appropriate product modifiers. The study number and the wording, "FOR AUTOLOGOUS USE ONLY" will be included in the label. In addition the label will have at least two unique identifiers such as the patient's alphanumeric identifier and birth date according to applicable regulations. Additional label elements required by local regulatory guidelines will also be included. Prior to the infusion, two individuals will verify all of this information, to ensure that the information is correctly matched to the patient, and that the patient receives only their autologous product.

6.6.2 Tisagenlecleucel supply and storage

Tisagenlecleucel cell product must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the tisagenlecleucel cell product should be stored according to the instructions specified on the product labels and in the [Investigator's Brochure] as well as the [Investigational Product Handling Manual].

6.6.3 Tisagenlecleucel compliance and accountability

Novartis has established methods to ensure full traceability between the patient's autologous leukapheresis and the tisagenlecleucel product in line with the requirements outlined in Regulation (EC) 1394/2007, the Directive 2004/23/EC as well as the rules and principles of the EU "Detailed guidelines on good clinical practice specific to advanced therapy medicinal Products" and 21 CFR1271.250 and 21CFR1271.290. The data contributing to the full traceability of the cells are stored for a minimum of 30 years. Any product quality complaints are documented by the clinical site and reported to the Novartis Clinical Supplies Quality Assurance (QA) Department. A unique patient identifier will be used in order to maintain the chain of identity between the autologous leukapheresis product and the tisagenlecleucel batch and the link between patient identity and unique patient identifier will be confirmed prior to infusion. The [Investigational Product Handling Manual] provides an overview of how the company ensures that the cells which are procured, processed, stored, and distributed by or on behalf of the Novartis can be traced from leukapheresis to infusion.

6.6.3.1 Tisagenlecleucel compliance

As a single administration study, compliance will be assessed by the investigator and/or study personnel and captured in the Drug Accountability Form.

6.6.4 Tisagenlecleucel disposal and destruction

For details on disposal and destruction of any unused tisagenlecleucel product or infusion supplies, please refer to the specific guidance provided in the [Investigational Product Handling Manual].

6.6.5 Handling of other study treatment

Not applicable.

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments through the end of the Treatment and Follow-up Phase (Section 7.1.1, Section 7.1.2, Section 7.1.3, and Section 7.1.4).

In the table, required assessments are indicated with an "X" at the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The tables indicate which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

No CRF will be used as a source document.

[redacted]

Table 7-1 Visit evaluation schedule

Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Obtain Informed Consent	D	7.1.1	X																				
IWRS/IRT Registration	S	6.5	X	X	X				X														
Demography	D	7.1.1	X																				
Inclusion/exclusion criteria	D	5.2 5.3	X																				
Medical history	D	7.1.1	X																				

[redacted]

Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Prior antineoplastic therapy	D	7.1.1	X																				
Prior/concomitant medications and non-drug therapies	D	6.4	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant antineoplastic therapies	D	6.4	X	X		X	X	X	X														

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**																
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**															**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**	
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**	
Antineoplastic therapies after tisagenlecleucel infusion	D	7.1.6								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Central confirmation of diagnosis	D	7.2.1	X																					
Diagnosis and extent of cancer and prognostic factors	D	7.1.1	X																					

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Physical examination	S	7.2.2.1	X					X	X	X		X		X		X	X	X	X	X	X	X	X	X
Performance status	D	7.2.2.4	X					X	X	X		X		X		X	X	X	X	X	X	X	X	X
Height	D	7.2.2.3	X																					
Weight	D	7.2.2.3	X				X		X								X	X	X	X	X	X	X	X
Vital signs	D	7.2.2.2	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry	D	7.2.2.2	X						X	X	X	X	X	X										

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**																
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**															**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**	
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**	
Cardiac imaging	D	7.2.2.6.2	X																					
Local Electrocardiogram (ECG)	D	7.2.2.6.1	X						X															
Leukapheresis	D	7.1.1		X																				
Lymphodepleting chemotherapy	D	7.1.2.1					X																	
Tisagenlecleucel infusion prerequisite assessment	S	7.1.2.3						X																

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Tisagenlecleucel infusion	D	7.1.3.1							X														
B-symptoms	D	7.2.1	X			X													X	X	X	X	X
PET-CT with contrast-enhanced diagnostic (Dx) CT – Neck, Chest, Abdomen, Pelvis	D	7.2.1	X			X if applicable													X, M3 and M6 only				

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
CT/MRI – Neck, Chest, Abdomen, Pelvis	D	7.2.1	X if no Dx PET-CT			X if no Dx PET-CT and if applicable													X if no Dx PET-CT	X	X	X	X
Dedicated PET	D	7.2.1	X if no PET CT			X if no PET-CT and if applicable													X if no PET-CT, only M3 and M6				

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**																
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**															**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Response (CR) confirmation by PET-CT or PET	D	7.2.1								Only for new CR and not previously documented, +/- 14 days from the CT image														
CT/MRI brain	D	7.2.1	As clinically indicated																					
Response evaluation per Lugano classification 2014	D	7.2.1	X			X if applicable													X	X	X	X	X	
Bone marrow biopsy or aspirate	D	7.2.1	X							only if new CR with a prior bone marrow involvement														

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
CSF cytology by lumbar puncture	D	7.2.1	As clinically indicated																				
Adverse events	D	8.1 8.2	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	D	7.2.2.5	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Flow cytometry before leukapheresis (peripheral blood)	D	7.1.1		X																			
Flow cytometry (leukapheresis product)	D	7.1.1		X																			
Pregnancy test - serum	S	7.2.2	X				X	X															X
Pregnancy test - urine	S	7.2.2															X	X	X	X	X	X	

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Pregnancies	S	8.4	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral serology	D	7.2.2.5	X			If > 8 weeks from screening																		
Coagulation	D	7.2.2.5	X						X			X		X			X							
Serum immunoglobulin levels	D	7.2.2.5	X											X			X		X					
Urinalysis	D	7.2.2.5	X				X		X								X							

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Rapid Influenza Testing	D	6.1.4.1 7.1.3 7.2.2.5				Within 10 days prior to infusion																	
Immunogenicity (humoral) – serum	D	7.2.3				X								X			X		X M3, M6, M12 only	X	X	X	
Immunogenicity (cellular) – peripheral blood	D	7.2.3				X								X			X		X M3, M6, M12 only	X	X	X	

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**														
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**													**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Serum cytokines (peripheral blood)	D	7.2.3 7.2.4				X		X		X	X	X	X	X	X	X	X		X M3 M6 M12 only				
[redacted]																							

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Phase			Screening			Pre-Treatment			Treatment and Follow-up															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**													**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
CRS assessments in peripheral blood (serum cytokines, inflammatory markers tisagenlecleucel PK)	D	7.2.3 7.2.4								As clinically indicated dependent upon the presence and time-course of CRS and administration of anti-cytokine therapies – refer to Table 7-7, Table 7-8, Table 7-13													

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**														**End of Study**
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**													
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
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Tisagenlecleucel cellular kinetics by qPCR (peripheral blood)	D	7.2.3				X			X	X	X	X	X	X	X	X	X	X M2 only	X	X	X	X	

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**														
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**													**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Tisagenlecleucel cellular kinetics by flow cytometry (peripheral blood)	D	7.2.3				X			X	X	X	X	X	X	X	X	X	X M2 only	X	X	X		
Tumor biopsy (CD19 expression, PD1, PDL1, Ki67)	D	7.2.3	X																as clinically indicated				

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Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**		**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**		**EOS +14d**
Tisagenlecleucel cellular kinetics - bone marrow (qPCR)	D	7.2.3	X																M3 and as clinically indicated					
Tisagenlecleucel cellular kinetics - bone marrow (flow cytometry)	D	7.2.3	X																M3 and as clinically indicated					

[redacted]

Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															**End of Study**
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
[redacted]																								
Peripheral blood (B cell and T cell levels– central assessment)	D	7.2.4				X		X				X	X	X			X		X M3 M6 M12 only	X	X		

[redacted]

Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Peripheral blood leukocyte transcriptional profiling	D	7.2.4				X		X				X		X			X							
RCL by VSV-g q-PCR (aliquots from tisagenlecleucel PK by qPCR)	D	7.2.2.5				X													X	X	X	X		

[redacted]

Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Leukapheresis sample for correlative studies	D	7.1.1.1		X																			
Tisagenlecleucel cell product sample for correlative studies (manufacturing site)	D	7.1.1.1				X																	

[redacted]

Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**		**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**	
Electronic patient reported outcomes (SF-36, version 2; EQ-5D-3L; FACT-Lym)	D	7.2.6	X																X	X	X		X
[redacted]																								
Disposition	D	7.1	X						(X)															X

[redacted]

Phase			**Screening**			**Pre-Treatment**			**Treatment and Follow-up**															
Visit	**Category**	**Protocol Section**	**Screening**	**Leukapheresis**	**Enrollment**	**Pre-lymphodepletion evaluation**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**														**End of Study**
Visit Number			**1**	**2**	**3**	**110**	**120**	**130**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**	**300,320, 330**	**310, 340,350, 360**	**370**	**380**	**390..**	**1999**
Study day			**W -10 to W -6**	**W -10 to W -8**	**W -6 to W -4**	**W -4 to D -8**	**D -6 to D -2**	**D -1**	**D 1**	**D 2**	**D 4 ±1 d**	**D 7 ±1 d**	**D 11 ±1 d**	**D 14 ±1 d**	**D 17 ±1 d**	**D 21 ±3 d**	**D 28 ±7 d**	**M 2, 4, 5, ±14d**	**M 3, 6, 9, 12 ±14d**	**M 18 ±14d**	**M 24 ±14d**	**Q6M ... (M30 ...) ±14d**	**EOS +14d**
Subject Status	D	n/a	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival follow-up	D	7.1.4							Every 3 months until end of the study. Refer to Protocol section 7.1.4															

[redacted]

7.1.1 Screening Phase

Patients must sign the IRB/EC approved ICF before any study specific screening procedures. Screening assessments to determine eligibility should be performed as per the visit evaluation schedule detailed in Table 7-1.

Patients who have signed an informed consent will be registered in the IRT system and undergo a routine lymphoma staging workup including all screening assessment outlined in Table 7-1. For detailed screening procedures, related to the use of Interactive Response Technology (IRT), please refer to the [IRT User Manual].

The assessments below do not need to be repeated if performed as part of clinical routine within the periods defined below:

- Serum immunoglobulin levels as per Table 7-5 within 6 weeks of the ICF signature
- Viral serology as per Table 7-5 within 6 weeks of the ICF signature
- Bone marrow biopsy within 6 months of the ICF signature provided that there are no symptoms or laboratory abnormalities suggesting bone marrow involvement by lymphoma
- LVEF assessment by ECHO/MRI or MUGA within 6 months of the ICF signature provided that there are no clinical symptoms of impaired cardiac function

7.1.1.1 Leukapheresis

Leukapheresis will be scheduled for cell procurement prior to final enrollment. It is strongly recommended to schedule leukapheresis prior to any planned chemotherapy or non-physiologic dose of steroids as an absolute T-cell count (absolute lymphocyte count multiplied by the percentage of CD3 positive lymphocytes) $\leq 300/mm^3$ may result in a poor T-cell collection and manufacturing failure.

Cryopreserved non mobilized leukapheresis products collected prior to study entry (historical) may be usable for manufacturing if collected at a certified leukapheresis center and if the product is accepted for manufacturing.

Please refer to the Leukapheresis Key Requirements within the most recent [Leukapheresis, Cryopreservation & Scheduling Manual] for more detailed instructions on optimal timing of leukapheresis collection and the recommended procurement, handling and shipment procedures of the leukapheresis samples to the designated manufacturing facility

Flow cytometry should be performed before leukapheresis in peripheral blood and post leukapheresis on leukapheresis product (i.e. ALC, absolute $CD45^+/CD3^+$, $CD45^+/CD3^+/CD28^-/CD27^-$, $CD4^+/CD25^+$, $CD45^+/CD14^+$).

Viably frozen samples from the leukapheresis material as well as the tisagenlecleucel product will be collected at the manufacturing site for correlative studies.

The date of Leukapheresis will be registered in the IRT system.

For patients who undergo leukapheresis collection on study after signing ICF, the following criteria must be met prior to leukapheresis collection:

[redacted]

Peripheral blood absolute lymphocyte count (ALC) ≥ 500/µL ($0.5x10^9$/L), or if ALC < 500/µL (<$0.5x10^9$/L), then the absolute CD3 lymphocyte count must be ≥ 150/µL

Please also refer to the [Leukapheresis, Cryopreservation & Scheduling Manual] for further details on the requirements prior to leukapheresis collection.

7.1.1.2 Re-screening

A patient who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the re-test result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within approximately 3 weeks of the original screening visit date. In this case, the patient will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 3 weeks of the original screening visit, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, and the patient will be assigned a new patient ID. All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

7.1.1.3 Enrollment

Following informed consent, information on the patient's leukapheresis product including sample sentinel vials collected from leukapheresis (when available) will be sent to Novartis manufacturing separately or together with leukapheresis product. Final enrollment is defined as the point at which a patient meets all clinical inclusion/exclusion criteria and the patient's leukapheresis product is received and accepted for manufacturing. The patient is then enrolled using the same Subject Number assigned at screening by the site investigator or designated staff. Once assigned, the Subject Number must not be reused for any other patient and the Subject Number for that individual must not be changed. If a screened patient is not enrolled for any reason, the specific reason will be entered into the clinical database.

Enrollment will be entered in the IRT system. For detailed enrollment procedures, related to the use of Interactive Response Technology (IRT), please refer to the [IRT User Manual]. A Disposition CRF should be completed indicating the date of enrollment and the specific reason if a patient is not enrolled as applicable.

7.1.1.4 Information to be collected on patients not enrolled (screen failure)

The reason for not being enrolled will be entered in the clinical database. The demographic information, informed consent, Inclusion/Exclusion pages, Leukapheresis information and any adverse events leading to patient discontinuation and death information (if applicable) must also

be completed for patients not enrolled. No other data will be entered into the clinical database for patients who are not enrolled.

7.1.2 Pre-treatment phase

For details of assessments, refer to Table 7-1.

Note: All patients must undergo a rapid influenza diagnostic test within 10 days prior to the planned CLT019 infusion. See Section 6.1.4.1.

7.1.2.1 Pre-lymphodepletion evaluation visit (W-4 to D-8)

Before the scheduled lymphodepleting chemotherapy regimen is to begin, the patient will undergo blood and urine collection for safety [redacted] humoral & cellular immunogenicity and RCL by VSV-G qPCR. In addition, adverse events and prior/concomitant medications will be reviewed. Imaging assessments will be performed as described in Table 7-2.

7.1.2.2 Lymphodepleting chemotherapy visit (D-6 to D-2)

Prior to tisagenlecleucel infusion, each patient should receive lymphodepleting chemotherapy. Please refer to Section 6.1.3 for information regarding lymphodepleting chemotherapy regimen and timing. If lymphodepleting chemotherapy is **NOT** required (for criteria please refer to Section 6.1.3), a visit should still occur during this time window, and required assessments according to Table 7-1 should be completed.

For patients who do receive lymphodepleting therapy, this visit should occur within 24 hours of starting lymphodepleting chemotherapy.

Final tisagenlecleucel infusion pre-requisites (including an ECG and a rapid influenza test) will be checked prior to infusion as per Section 6.1.4.1.

7.1.2.3 Pre-infusion visit (D-1)

On the day prior to the scheduled tisagenlecleucel infusion, patients will undergo assessments as described in Table 7-1.

If at this point the patient does not enter the Treatment phase, this must be indicated in the IRT system.

7.1.3 Treatment and Follow-up Phase

7.1.3.1 Infusion visit (D1)

Tisagenlecleucel infusion will begin 2 to 6 days after completion of lymphodepleting chemotherapy.

A single dose of 0.6 to 6 x 10^8 CAR-positive viable T cells will be administered to the patient.

Vital signs (temperature, respiration rate, pulse, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion and then approximately every 15

[redacted]

minutes for one hour and then every hour for the next two hours, or until these signs are satisfactory and stable.

An additional blood sample will be collected post-infusion for tisagenlecleucel cellular kinetics assessment as per Table 7-1.

Details on the administration of the tisagenlecleucel infusion are found in Section 6.1.4.3.

The tisagenlecleucel infusion visit must be registered in the IRT system.

7.1.3.2 Post-tisagenlecleucel infusion visits: D2 to M2±14d

Following CT019 infusion, patients will undergo assessments as per Table 7-1.

Weekly (or more frequent, see Table 7-1) sample collections for serum cytokines, tisagenlecleucel cellular kinetics, and inflammatory markers (e.g. ferritin and CRP) are mandated during the first 28 days following tisagenlecleucel infusion. However, as the time-course and rapidity of CRS development varies among patients, additional unscheduled samples for these markers may also be collected as needed, if it is clinically feasible. Frequent monitoring of serum CRP, ferritin and cytokines should be considered during the clinical course of CRS of any severity (e.g. every day to several days) especially around the following clinical events: initial persistence of fevers, hemodynamic instability, initial and worsening of respiratory distress, rapid clinical deterioration, just prior to and daily for 2 days following tocilizumab administration, around other clinically significant events and upon the clinical resolution of CRS.

Please note that results of cytokine analyses are NOT to be used for clinical management decisions of CRS. A detailed treatment algorithm has been established with clear criteria for CRS management (see Table 6-1 and Table 6-2).

7.1.3.3 Post-tisagenlecleucel infusion visits: M3±14d to M24±14d, Q6M... ±14d

At the intervals listed in the Table 7-1, patients will undergo assessments including disease response evaluation with efficacy assessment sent to IRC for review.

If at any of these visits the patient has a radiological CR based upon imaging assessments, a bone marrow biopsy or aspirate needs to be performed in patients that had prior bone marrow involvement to confirm the CR.

If at any of these visits the patient is confirmed to have relapse or disease progression, no further imaging assessments [redacted] (see Section 7.2.1 and Section 7.2.4). Patients will continue to be followed for safety according to the assessments described in Table 7-1. Cellular kinetic sampling will only continue to assess B- and T-cell levels, transgene persistence, and immunogenicity. For details please refer to Section 7.2.3. Assessments of patient-reported outcomes (SF-36 version 2; EQ-5D-3L; FACT-Lym) will be continued for the next two visits as per Table 7-1 (see Section 7.2.6).

Note: For patients with tisagenlecleucel transgene levels equal to or greater than 1% of WBC:

If ≥ 1% of the WBC in peripheral blood are positive for CD19 CAR vector sequences by qPCR at > 12 months from tisagenlecleucel infusion, then the patient will be asked to return for a confirmatory blood test prior to the next 6 month visit. If ≥1% of the WBC is positive upon the

[redacted]

receipt of the confirmatory qPCR result, then the genomic vector integration sites will be determined. Identified vector integration sites will be evaluated using bioinformatic approaches to determine the frequency of integration events in regions with known relationships to human cancers (i.e. near oncogenes). If integration site analysis reveals mono- or oligo-clonality pattern and/or integration at or near an oncogenic locus, a monitoring plan, including follow-up molecular analyses, will be developed in collaboration between the Investigator, Sponsor and Health Authorities that is specific for the health care risks that are anticipated given the nature of the integration site and vector target cell type.

7.1.3.4 End of study visit

The End of Study (EOS) visit for each patient will be at the time when all patients have completed their Month 24 evaluation or discontinued prematurely. Patients who have completed their Month 24 visit before the end of the study will be followed for assessments at onsite visits every 6 months (Q6M) until the end of the study. See Section 4.3 for more information. During the EOS visit patients will undergo the assessments specified in Table 7-1, and a Disposition CRF should be completed. Following the EOS visit, patients will be enrolled in the LTFU study [CCTL019A2205B].

7.1.4 Survival follow-up

For all patients who receive a tisagenlecleucel infusion, follow-up for survival every 3 months until end of study is required. If a patient misses a quarterly scheduled visit where survival status is required, or if the quarterly time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact. After the end of this study, patients will continue to be followed for survival under the LTFU protocol [CCTL019A2205B].

7.1.5 Discontinuation of study treatment

Tisagenlecleucel infusion may be discontinued if, in the investigator's opinion, its continuation would be detrimental to the patient's safety. Patients who discontinue from tisagenlecleucel treatment should NOT be considered withdrawn from the study and should continue to be followed as per assessment schedule provided in Table 7-1. A Disposition CRF should be completed.

If for any reason a patient is discontinued from study treatment while or after receiving lymphodepleting chemotherapy and before the scheduled infusion of tisagenlecleucel, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Study visit will be performed. A Disposition CRF should be completed, giving the date and reason for stopping the Study.

7.1.6 Discontinuation from study

Patients may voluntarily withdraw from the study or be withdrawn from the study at the discretion of the investigator at any time.

[redacted]

If a patient discontinues early from the study, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Study visit will be performed. A Disposition CRF should be completed, giving the date and reason for stopping the Study.

Patients may be withdrawn from the study if any of the following occur:

- The patient is lost to follow-up
- Patient noncompliance with study therapy and/or clinic appointments
- Voluntary withdrawal; a patient may remove himself/herself from the study at any time without prejudice.
- Termination of the study by the sponsor or the health authorities

7.1.7 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.8 Follow up for safety evaluations – Long-term follow-up study

As a single administration study, patients are followed on study for at least 2 years post-infusion for safety and efficacy evaluations. A long term post-study follow-up for lentiviral vector safety will continue under a separate destination protocol [CCTL019A2205B]. Patients will continue to be followed until 15 years post-tisagenlecleucel infusion as per health authority guidelines.

[redacted]

Under the long term follow-up protocol, semiannual and annual evaluations will be performed on all patients who have received a tisagenlecleucel cell product infusion as recommended by the FDA and EMA in accordance with the relevant guidelines. All patients who either complete or prematurely discontinue from the study will be enrolled in this destination protocol at the time of study completion/discontinuation. A separate informed consent/assent forms will be provided for this protocol. One to two times a year patients will visit the clinical site for a physical exam and medical history (including concomitant medications and adverse events) with careful attention to features possibly related to lentiviral associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, or new incidence of other hematologic disorders. In addition, labs will be drawn to evaluate routine safety endpoints, tisagenlecleucel vector persistence and RCL.

7.1.9 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the Study Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments will be performed as indicated in Table 7-2 until disease progression or relapse, start of another anticancer therapy, death, lost to follow-up or withdrawal of consent. Efficacy will be evaluated by an Independent Review Committee (IRC) using the Lugano classification 2014 (Cheson et al 2014; Barrington et al 2014) as detailed in Appendix 14.1. The latest efficacy assessments after bridging therapy and prior to infusion will be used as baseline.

Radiological imaging will be transmitted by the sites to the imaging Contract Research Organization (CRO) designated by Novartis to undergo quality checks and central review by the IRC. Clinical data such as, physical exam, bone marrow results, pathology/histology and cytology results; as well as, information regarding prior interventions, pre-existing radiographic findings that may mimic lymphoma at screening/Pre-lymphodepletion evaluation (pre-infusion) and on-study interventions will be transmitted to the imaging CRO for review by a medical oncologist/hematologist. At IRC, during the overall review the available clinical data will be integrated with the pathological and radiological response data to provide the overall disease response:

The presence of one (1) or more stable, but persistent clinical lesions will downgrade a radiology CR to an overall PR.

The presence of one (1) or more new or worsening clinical lesions will result in Overall PD.

[redacted]

If bone marrow biopsy is not negative, a radiographic TPR of CR at that time point would be downgraded to an overall PR.

A new lesion biopsy result indicating a malignancy would result in overall PD, if not already assessed as PD during the radiology review.

For any given time point, any clinical listings that are within a +14 day window (+28 day window for bone marrow data) of the radiographic time point date can be used for the corresponding oncology time point assessments. Clinical listings that are +15 days after a radiographic time point will be grouped with the next radiographic time point. For example, if the radiographic time point date is 01Mar, and the non-bone marrow clinical evaluations on the listings occur on 10Mar and 16Mar, the listings from 10Mar will be associated with the radiographic time point date of 01Mar. The listings from 16Mar will not be associated with the 01Mar radiographic time point and will be grouped with the next radiographic time point. Any clinical listings that fall outside the allowable window will be evaluated with the next radiographic time point. A definition of assessment date is provided in Appendix 1, Section 14.1.4.5.3.

For bone marrow data, the assessment window will be extended to +42 days if there are no subsequent radiographic time points. This +42 day window will only apply to overall assessments associated with the patients's last radiographic time point.

Further details regarding the IRC will be provided in the IRC charter. The decision regarding patient management will remain with the local investigator. Eligibility will be determined by local assessment of the required images obtained during screening. Imaging studies used to determine eligibility must be submitted to the IRC.

Disease status at baseline and efficacy during the study will be evaluated using the following:

- Lesions from physical exam findings
- Pathology assessment
- Imaging
- Bone marrow biopsy or aspirate
- CSF cytology
- Procedures (e.g surgeries) performed on study

The results of the IRC assessment will be used for primary and secondary analysis purposes. Any imaging assessments already completed during the regular work-up of the patient within 8 weeks prior to start of infusion, including before signing the main study ICF, may be considered as the pre-infusion images for this study. Any imaging assessments obtained after infusion cannot be considered pre-infusion images.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable (non-index) lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

[redacted]

Imaging Assessments

Imaging assessments will be performed at screening and within 8 weeks from screening imaging to infusion or if bridging chemotherapy was given. Baseline/Pre-infusion imaging assessment should be done as close to infusion as possible. In the event more than one imaging assessment is performed after ICF and prior to infusion then the assessment dated closest to infusion will be used as baseline/pre-infusion.

Any imaging assessments already completed during the regular work-up of the patient within 8 weeks prior to infusion, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after infusion cannot be considered baseline images. The patient should not receive any anticancer therapy between the screening images and infusion. One of the following assessments are required at screening and/or baseline, month 3 and Month 6 and at other timepoints only for new CR on CT scan not previously documented to confirm response:

PET-CT with diagnostic CT (or PET-CT without diagnostic CT + dedicated diagnostic CT/MRI or dedicated CT/MRI of diagnostic quality + dedicated PET when PET-CT with diagnostic contrast-enhanced CT is not available) must be performed at screening, Months 3, 6 and prior to or after Months 3/6 only for new CR not previously documented to confirm response. The CT component of the PET-CT may be used in lieu of a standalone CT/MRI, only if the CT component is of similar diagnostic quality as a contrast enhanced CT performed without PET.

If a contrast enhanced PET-CT with diagnostic CT is not available, a PET (using a PET-CT without diagnostic CT or a dedicated PET scanner) must be performed and a dedicated contrast-enhanced diagnostic CT/MRI should be performed in addition to the FDG-PET scan. If independent CT and PET scanners are used, and both scans are to be done on the same day, the PET must be performed prior to the contrast-enhanced CT as to not compromise PET results. The PET-CT acquisition methodology (e.g., administration of intravenous contrast) should remain consistent between baseline, Months 3, 6, 9, 12, 18, 24, Q6M (if applicable), and EOS for any given patient.

PET imaging is always required in order to confirm the first documented complete response (CR). If the first documented radiological CR is seen on CT scan only, a confirmatory PET scan (either FDG PET or PET-CT) should be obtained within 14 days in order to confirm that timepoint's response of CR. If the PET scan is not obtained within 14 days, the timepoint must be assessed as a PR, and the next scan should be done by one of the 3 methods above as soon as possible to confirm the CR. Once CR has been established by PET imaging, subsequent CR and/or PD may be followed by CT imaging only.

The possible scanning scenarios that are to occur are:

1. PET-CT with diagnostic CT
2. PET-CT with non-diagnostic CT + dedicated diagnostic CT/MRI
3. Dedicated diagnostic CT/MRI + dedicated FDG PET

It is preferred to obtain a PET-CT with diagnostic CT at all protocol required imaging visits when possible.

If a patient is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the neck and chest (MRI is

[redacted]

not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Brain MRI or CT should be completed if clinically indicated at screening and post infusion. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

If skin lesions are present as a result of a physical exam, these are to be documented via the Lugano classification 2014 assessment as a physical exam, skin lesion.

If EOS is performed outside of the scheduled study visits, efficacy assessments only have to be performed if the last assessment was done >30 days before this visit.

Additional imaging assessments for suspicion of PD or to support efficacy evaluation may be performed at any time during the study at the investigator's discretion. If imaging is done for safety reasons only there should be no efficacy assessment and/or submission to the imaging CRO. (All imaging submitted to the imaging CRO are expected to have a corresponding local efficacy assessment).

Any on protocol scheduled and/or unscheduled imaging assessments done within +/- 14 day window are to be assessment under a single evaluation.

Clinical suspicion of disease progression at any time requires prompt physical examination and imaging without waiting for the next scheduled imaging assessment. It is recommended to verify disease progression by CT and tumor biopsy, if applicable (see Table 7-2).

Once disease progression has been confirmed, no further efficacy assessments will have to be performed.

Table 7-2 Imaging or Disease Assessment Collection Plan

Procedure	Screening	Pre-infusion	Post-infusion Assessment
PET-CT with diagnostic (Dx) contrast enhanced CT (Neck, Chest, Abdomen, Pelvis)	Mandated	Mandated if >8 weeks from screening imaging to infusion or if bridging chemotherapy" was given	Mandated at Months 3, 6 and at any visit a new CR by CT needs to be confirmed, not seen previously Once CR is confirmed with PET, additional PET imaging is not required (CT only)
CT/MRI (Neck, Chest, Abdomen, Pelvis)	Mandated if PET-CT with diagnostic CT is not available	Mandated if >8 weeks from screening imaging to infusion or if bridging chemotherapy" was given and if PET-CT with diagnostic CT is not available	Mandated at Months 9, 12, 18, 24, Q6M (if applicable), EOS and any time to confirm PD or relapse Mandated at Month 3, 6 and at any visit a new CR by CT needs to be confirmed, not seen previously, if PET-CT with diagnostic CT is not available PET-CT with diagnostic CT is preferred at all imaging visits when possible

[redacted]

Dedicated PET	Mandated if PET-CT is not available	Mandated if >8 weeks from screening imaging to infusion or if bridging chemotherapy" was given and if PET-CT is not available	Mandated at Months 3 and 6 if PET-CT is not available Any new visit a new CR by CT needs to be confirmed, not seen previously Once CR is confirmed with PET, additional PET imaging is not required (CT only)
Response (CR) confirmation by PET-CT or PET	NA	NA	PET imaging is required +/- 14 days within the same CT timepoint window when CR is seen by CT, only for new CR and not previously documented. Once CR has been confirmed PET imaging is no longer needed however remains the preferred method when possible.
CT/MRI Brain	As clinically indicated	As clinically indicated	As clinically indicated
Bone marrow biopsy or aspirate FL cells	Mandated	NA	Mandated at time of Complete Response if BM was involved prior to treatment and as clinically indicated
CSF Cytology	As clinically indicated	As clinically indicated	As clinically indicated
Tumor biopsy (FFPE) for pathology and molecular assessment	Mandated	NA	NA
[redacted]			

**Bridging therapy consisting of steroids only does not require additional imaging before infusion

7.2.1.1 PET Imaging-Five Point Scale

To standardize PET interpretation, a simple reproducible scoring method called the five point scale (5PS) or the Deauville criteria has been implemented for initial staging and assessment of interim and end of treatment responses. The 5PS assesses the most intense uptake in a site of disease.

Table 7-3 Five Point Scale (5PS)

Score	Findings
Score 1	No uptake above background
Score 2	Uptake ≤ mediastinum
Score 3*	Uptake > mediastinum, but ≤ liver
Score 4**	Uptake moderately > liver
Score 5**	Uptake markedly higher than liver and/or new lesions

* Score 3 will be considered PET negative for this study

**Score 4 should be applied to uptake greater than the maximum standard uptake value (SUV) in a large region \ of normal liver and score 5 to uptake 2 times greater than the maximum SUV in the liver. PET images should be converted to SUV maps to support comparison across time points and to standardize viewing conditions.

[redacted]

Score	Findings
(New) areas of uptake unlikely to be related to lymphoma will be marked as "X" (Barrington et al. 2014).	

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing various parameters including physical examination, ECG, and vital signs, immunogenicity against tisagenlecleucel, lab abnormalities and collecting AEs through Month 12. After Month 12 only selected AEs will be collected. For complete details on AE collection, reporting and adverse events of special interest, refer to Section 8.

For all patients, any pregnancies will need to be reported and followed up.

7.2.2.1 Physical examination

A complete evaluation will generally include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History CRF page. Any lesions, detected during a physical exam at any time-point that are not detectable by imaging should be recorded on the Tumor Evaluation CRF page as a non-targeted lesion and does not need to be recorded on the Adverse Event CRF page. Significant new findings, other than new lesions, that begins or worsens after informed consent must be recorded on the Adverse Event CRF page.

7.2.2.2 Vital signs

Vital signs include temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry. They should be assessed according to Table 7-1 and Section 6.1.4.3.

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.4 Performance status

At visits according to Table 7-1, the ECOG performance scale index will be used to evaluate the performance status of the patients.

Table 7-4 ECOG Performance status grade

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

[redacted]

Grade	ECOG
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

7.2.2.5 Laboratory evaluations

Laboratory assessments described in Table 7-5 and Table 7-6 will be performed according to appropriate VES (Table 7-1). Note: Additional assessments should be performed between visits as clinically indicated and to follow AEs or tisagenlecleucel expected events. For all laboratory assessments that occur on Day 1, these should be performed prior to tisagenlecleucel infusion unless indicated otherwise.

Table 7-5 Local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCHC, MCV, Platelets, Red blood cells, White blood cells with complete differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, bands, other)
Chemistry	Glucose (fasting/non-fasting), Blood Urea Nitrogen (BUN), Creatinine, eGFR, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Magnesium, Phosphorus, LDH, Ferritin,CRP, and Uric Acid
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes, Nitrite, pH, Protein, Specific Gravity)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR), activated Partial thromboplastin time (aPTT), fibrinogen, and D-dimer
Pregnancy screen	Urine and serum tests as outlined in Section 7.2.2.8. Note, if urine test is positive, a serum test has to be performed for confirmation
Influenza	Rapid Influenza A & B Test
Viral Serology	Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), Hepatitis surface antibody (HBsAb), Hepatitis C Virus (HCV) antibody, HIV antibody (if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines)
Serum Immunoglobulin levels	IgG, IgA, IgM

Table 7-6 Central clinical laboratory parameters collection plan

Test Category	Test Name/Method
CD19 testing	Immunohistochemistry or flow cytometry
Follicular lymphoma histology confirmation and grade determination	Histology
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Bone marrow aspirate/biopsy	Flow cytometry or immunohistochemistry
B cell and T cell levels	Flow cytometry (peripheral blood)
RCL (VSV-G)	VSV-g q-PCR (whole blood)
Cytokines	Serum cytokine panel, PD1, PDL1 (peripheral blood)

[redacted]

Test Category	Test Name/Method
Immunogenicity	Presence of immunogenicity (cellular/humoral) pre/post-tisagenlecleucel infusion
Tisagenlecleucel cellular kinetics	Tisagenlecleucel PK by q-PCR or flow cytometry (peripheral blood, bone marrow aspirate)
[redacted]	[redacted]
Persistence of CLT019 transgene sequences in relevant tissues	Tisagenlecleucel transgene by qPCR
[redacted]	[redacted]
[redacted]	[redacted]
Additional assessments	Flow cytometry on pre-leukapheresis peripheral blood and leukapheresis product (ALC, absolute $CD45^+/CD3^+$, $CD45^+/CD3^+/CD28^-/CD27^-$, $CD4^+/CD25^+$, $CD45^+/CD14^+$).

Refer to the [Laboratory Manual] for more detailed instructions for the collection, handling, and shipment of PK [redacted] samples.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard local 12 lead ECG will be performed at:

- Screening
- Infusion-Day 1 (prior to tisagenlecleucel infusion)

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate

7.2.2.6.2 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

A MRA, MUGA or ECHO scan is required to be completed at screening. Clinically significant abnormalities present when the patient signed the informed consent should be reported as Medical History on the appropriate CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded as an Adverse Events on the CRF page. Patients must have a left ventricular ejection fraction (LVEF) $\geq$ 45% to be included into the study.

7.2.2.7 Pregnancy assessments

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. For the frequency of pregnancy testing and type of sample (serum or urine) please refer to Table 7-1. Pregnancy testing is required within 24 hours prior to leukapheresis procedure,

[redacted]

lymphodepletion and prior to tisagenlecleucel infusion. Following tisagenlecleucel infusion, monthly urine pregnancy tests will then be required to be performed until Month 12 and until CAR T-cells are no longer present by qPCR on two consecutive tests (as per Table 7-1). At this time, a serum pregnancy test should be performed. A serum pregnancy test will also be required at the End of Study visit. Women of child-bearing potential will be tested for pregnancy monthly via a urine test either at their scheduled Visit or they perform at-home urine pregnancy testing monthly using kits provided.

Women of child-bearing potential will be instructed to contact the site immediately at any time during the study should they have a positive pregnancy test. In case of positive urine pregnancy testing, - additional testing must be performed to confirm pregnancy and if confirmed follow reporting requirements as described in Section 8.4.

For more information about the effects of tisagenlecleucel on reproduction please refer to the recent [Investigator's Brochure].

7.2.3 Pharmacokinetics

Blood and bone marrow samples will be collected from all patients for the assessment of tisagenlecleucel transgene levels by qPCR and the tisagenlecleucel transduced cells by flow cytometry of CD3-positive cells. Blood samples will be collected at the time points indicated in Table 7-7 and Table 7-8 while bone marrow aspirates will be collected as indicated in Table 7-9 and 7-10. Sampling times are relative to date and time of tisagenlecleucel infusion unless otherwise specified. The exact date and actual time of blood sampling must be recorded on the appropriate CRF pages. All samples will be used for PK evaluations and estimation of cellular kinetic parameters as detailed in Section 10.5.4. Levels of tisagenlecleucel transgene and tisagenlecleucel transduced cells will be summarized as detailed in Section 10.5.4.

7.2.3.1 Pharmacokinetic blood collection and handling

Refer to the [Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK and cellular kinetics samples.

Table 7-7 Tisagenlecleucel cellular kinetics by q-PCR in peripheral blood collection log

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	PK1 Sample No. (tisagenlecleucel)	Blood Volume (mL)
W-4 to D-8 Pre-Lymphodepletion evaluation	D-8 (0h Pre-dose)[a]	111	201	4
D1 (10 minutes ± 5 minutes post-infusion)	D1 (10 min post-dose ±5 min)	111	202	4
D2	D2 (24h post- dose +/-6h)	111	203	4
D4±1d	D4	111	204	4
D7±1d	D7	111	205	4
D11±1d	D11	111	206	4
D14±1d	D14	111	207	4
D17±1d	D17	111	208	4

[redacted]

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	PK1 Sample No. (tisagenlecleucel)	Blood Volume (mL)
D21±3d	D21	111	209	4
D28±7d	D28	111	210	4
M2±14d	D60	111	211	4
M3±14d	D90	111	212	4
M6±14d	D180	111	213	4
M9±14d	D270	111	214	4
M12±14d	D360	111	215	4
M18±14d	D540	111	216	4
M24±14d	D720	111	217	4
Q6M[a]		111	1001	4
Unscheduled PK samples related to CRS[b]		111	2001	4
Unscheduled (PK samples related to safety events, relapse) [c,d]		111	3001	4

*All measurement times are relative to date of tisagenlecleucel infusion unless otherwise specified.
** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible. See Section 7.1.3
[a]PK samples from all patients in follow-up Q6M visits beyond M24 till EOS are uniquely, sequentially numbered 1001, 1002, etc.
[b]Unscheduled PK samples related to a CRS events whereby Tocilizumab is not administered are uniquely, sequentially numbered 2001, 2002, etc [redacted]
[c]Unscheduled PK samples related to other non-CRS safety events are uniquely, sequentially numbered 3001, 3002, etc.
[d]In the event patient relapses or starts a new treatment, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-11 and Table 7-12)

Table 7-8 Tisagenlecleucel cellular kinetics by flow cytometry in peripheral blood collection log

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	PK2 Sample No. (tisagenlecleucel)	Blood Volume (mL)
W-4 to D-8 Pre-Lymphodepletion evaluation	D-8	111	301	2
D1 10 minutes ± 5 minutes post-infusion	D1 (10 min post-dose ±5 min)	111	302	2
D4±1d	D4	111	303	2
D7±1d	D7	111	304	2
D11±1d	D11	111	305	2
D14±3d	D14	111	306	2
D17±1d	D17	111	307	2
D21±3d	D21	111	308	2
D28±7d	D28	111	309	2

[redacted]

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	PK2 Sample No. (tisagenlecleucel)	Blood Volume (mL)
M2±14d	D60	111	310	2
M3±14d	D90	111	311	2
M6±14d	D180	111	312	2
M9±14d	D270	111	313	2
M12±14d (EOS)	D360	111	314	2
M18±14d	D540	111	315	2
M24±14d	D720	111	316	2
Unscheduled PK samples related to CRS[a]		111	4001	2
Unscheduled (PK samples related to safety events, relapse) [b,c]		111	5001	2

*All measurement times are relative to date of tisagenlecleucel infusion unless otherwise specified.
** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible. See Section 7.1.3
[a]Unscheduled PK samples related to a CRS events whereby tocilizumab is not administered are uniquely, sequentially numbered 4001, 4002, etc [redacted]
[b]Unscheduled anytime PK samples related to other non-CRS safety events will be uniquely, sequentially numbered 5001, 5002, etc.
[c]In the event patient relapses or starts a new treatment, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-11 and Table 7-12)

Table 7-9 Tisagenlecleucel cellular kinetics by q-PCR in bone marrow aspirate collection log

To be completed only if bone marrow examined

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	PK3 Sample No. (tisagenlecleucel)	Sample Volume (mL)
W-10 to W-6 Screening	Pre-dose	111	401	2
M3±14d	M3	111	402	2
Unscheduled (e.g. at time of radiological CR, related to relapse) [a]		111	6001	2

*All measurement times are relative to date of tisagenlecleucel infusion unless otherwise specified.
a. Unscheduled time points begin with 6001, 6002, 6003 series

Table 7-10 Tisagenlecleucel pharmacokinetics by flow cytometry in bone marrow aspirate collection log

To be completed only if bone marrow examined

[redacted]

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	PK4 Sample No. (tisagenlecleucel)	Sample Volume (mL)
W-10 to W-6 Screening	Pre-dose	111	501	2
M3±14d	M3	111	502	2
Unscheduled (e.g. at time of radiological CR, related to relapse) [a]		111	7001	2
*All measurement times are relative to date of tisagenlecleucel infusion unless otherwise specified. a. Unscheduled time points begin with 7001, 7002, 7003 series..."				

Table 7-11 Immunogenicity (humoral) serum sample collection log

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	IG1 Sample No. (tisagenlecleucel)	Sample Volume (mL)
W-4 to D-8 Pre-Lymphodepletion evaluation	Pre-dose	111	601	3
D14±1d	D14	111	602	3
D28±7d	D28	111	603	3
M3±14d	D90	111	604	3
M6±14d	D180	111	605	3
M12±14d	D360	111	606	3
M18±14d	D540	111	607	3
M24±14d	D720	111	608	3
Q6M[a]		111	6601	3
Unscheduled (e.g. related to relapse)[b,c]		111	8001	3
*All measurement times are relative to date of tisagenlecleucel infusion unless otherwise specified. [a]IG1 samples from all patients in follow-up Q6M visits beyond M24 till EOS are uniquely, sequentially numbered 6601, 6602, etc. [b]Unscheduled anytime PK samples related to other non-CRS safety events will be uniquely, sequentially numbered 8001, 8002, etc. [c]In the event patient relapses or starts a new treatment, an unscheduled immunogenicity sample should be collected along with corresponding PK sample (refer to Table 7-7, Table 7-8)				

Table 7-12 Immunogenicity (cellular) whole blood sample collection log

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	IG2 Sample No. (tisagenlecleucel)	Sample Volume (mL)
W-4 to D-8 Pre-Lymphodepletion evaluation	Pre-dose	111	701	10
D14±1d	D14	111	702	10
D28±7d	D28	111	703	10

[redacted]

Day*	Scheduled time point relative to dosing	DRID (tisagenlecleucel)	IG2 Sample No. (tisagenlecleucel)	Sample Volume (mL)
M3±14d	D90	111	704	10
M6±14d	D180	111	705	10
M12±14d	D360	111	706	10
M18±14d	D540	111	707	3
M24±14d	D720	111	708	3
Q6M[a]		111	7701	3
Unscheduled (e.g. related to relapse)[b,c]		111	9001	10

*All measurement times are relative to date of tisagenlecleucel infusion unless otherwise specified.

[a]IG2 samples from all patients in follow-up Q6M visits beyond M24 till EOS are uniquely, sequentially numbered 7701, 7702, etc.

[b]Unscheduled anytime PK samples related to other non-CRS safety events will be uniquely, sequentially numbered 9001, 9002, etc.

[c]In the event patient relapses or starts a new treatment, an unscheduled immunogenicity sample should be collected along with corresponding PK sample (refer to Table 7-7, Table 7-8)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.3.2 Analytical method

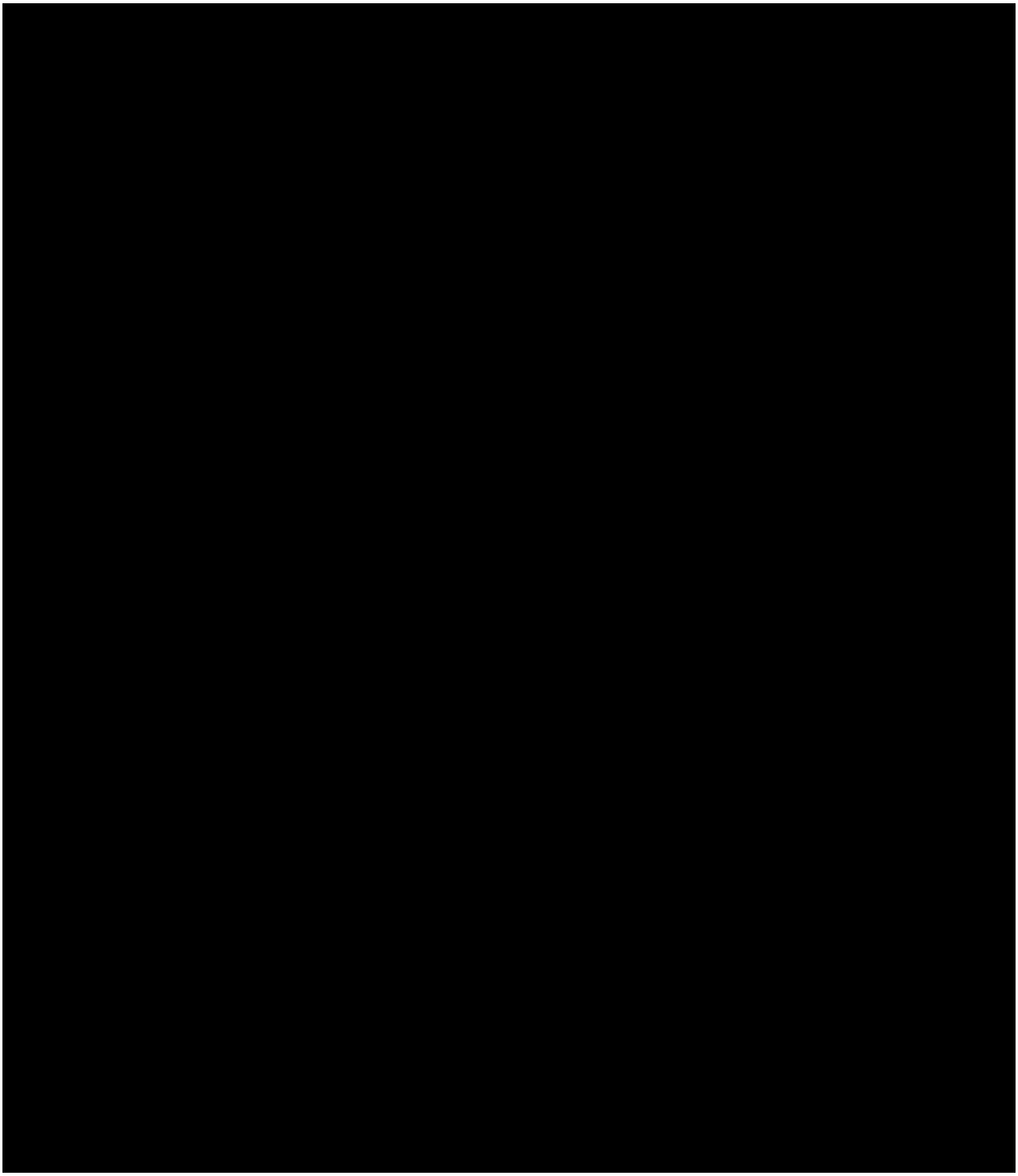
The quantitative polymerase chain reaction (qPCR) or flow cytometry methods will be used for estimation of cellular kinetics of tisagenlecleucel [SBP pALL-Section 1.6].

The entities measured are summarized below:

- CAR19 transgene levels as generated by q-PCR
- CAR-positive viable T cells measured by flow cytometry of CD3+
- CAR-positive viable T cells measured by flow cytometry of CD3+/CD8+ cells

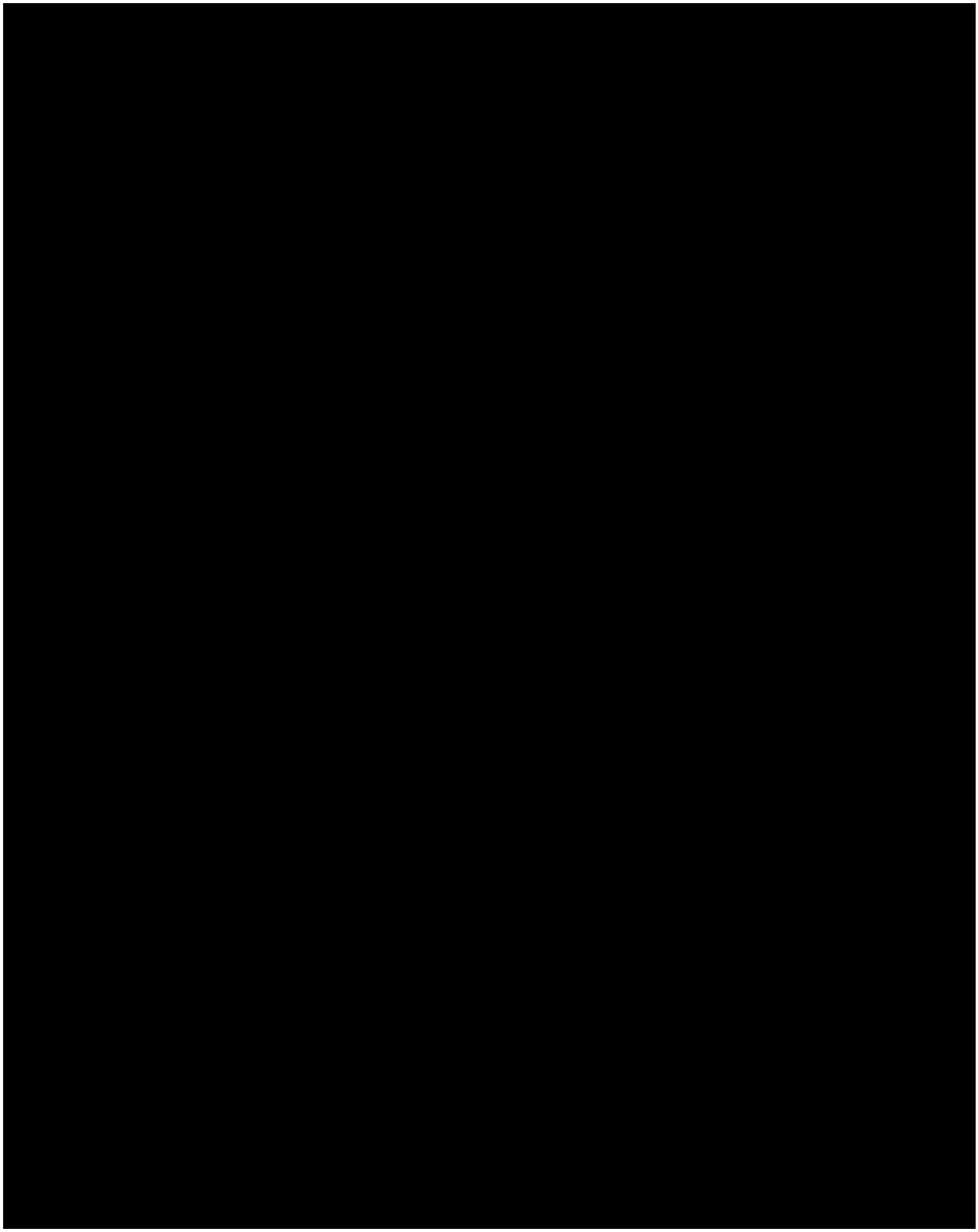
Additional details are provided in the bioanalytical data report [GDX-RPT-1292] [GDX-RPT-1243] [CTL019C2201-flow cytometry bioanalytical data report].

[redacted]



[redacted]

[redacted]



[redacted]

7.2.6 Patient reported outcomes (PRO)

Three questionnaires will be used in this study to capture patient reported outcomes (PROs) at the visits specified in Table 7-1: SF-36v2 (Acute Form), FACT-Lym and EQ-5D-3L. Brief description of each questionnaire is given in the sections below. For patients who relapse or progress, assessments of patient-reported outcomes (SF-36 version 2; EQ-5D-3L; FACT-Lym) will be continued for the next two visits as per Table 7-1.

[redacted]

PRO data will be collected by electronic devices (i.e. tablet). Each of the questionnaires described below is designed for patient self-administration. The method of activating and operating the data capture device is provided in a separate user guide.

The patient should be given the electronic device to complete the questionnaire(s) at the scheduled visit before other clinical assessments are conducted. The questions should be completed in the language the respondent is most familiar with, at the scheduled visit before the patient sees the investigator for clinical assessments. The patient should be given sufficient space and time to complete the questions.

The study coordinator should check the patients' responses for completeness and encourage the patient to complete any missing responses. Detailed instructions relating to the administrative procedures of the questionnaires will be provided to the sites. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system.

The completed ePRO data and any unsolicited comments made by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs, including SAEs, before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed ePRO data. Study investigators must follow reporting instructions outlined in Section 8.1.2.

7.2.6.1 FACT-Lym

The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) is a questionnaire to assess the quality of life in patients with Lymphoma. It consists of a general quality of life instrument (FACT-G) and a condition specific module Lym. The FACT-Lym is a fully validated QOL questionnaire applicable for patients with lymphoma and includes a module which assesses specific concerns of patients with lymphoma. 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 five subscales (Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being and Additional Concerns). The Lym module consists of 15 statements patients need to endorse on an identical five-point scale. This scale is designed for patient self-administration. Patients should be instructed to read the brief. After the patient's correct understanding has been confirmed they should be encouraged to complete every item in order without skipping any. Some patients may feel that a given question is not applicable to them and therefore will skip the item altogether. Patients should be encouraged to check the response most applicable.

7.2.6.2 SF-36 v2 (Acute form)

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed. The SF-36 has proven useful in monitoring general and specific populations, comparing the relative

burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients.

7.2.6.3 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 rate each of these items from "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire 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 approximately 5 to 10 minutes to complete.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the infusion of tisagenlecleucel.

The investigator has the responsibility for managing the safety of individual patient and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

[redacted]

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.2):

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, with the exception of CRS, which will follow Table 6-1. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, life-threatening and fatal, corresponding to Grades 1 - 5, will be used
2. its relationship to the study treatment and other investigational treatment If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a serious adverse events (SAE) (see Section 8.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.
6. All adverse events must be treated appropriately. Treatment may include treatment interruption or withdrawal.
7. its outcome, i.e., its recovery status or whether it was fatal

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history CRF.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for the duration as specified in Appendix 3 Section 14.3.1.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented as per Lugano guideline, should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will

be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the treatment.

Information about adverse drug reactions for the investigational drug can be found in the [Investigator's Brochure].

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease.

Detailed AE reporting requirements during the periods of screening, pre-treatment and treatment and follow-up are outlined in Appendix 3 Section 14.3.1.

8.1.2 Adverse Event of special reporting requirements

If specifically requested by a local Health Authority, expedited reporting of pre-specified AEs will occur.

8.1.3 Duration of adverse event reporting

Detailed guidance to determine whether or not a non-serious AE, an SAE, concomitant medication, or laboratory result has to be recorded in the eCRF during the relevant study period is provided in Appendix 3 (Section 14.3).

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening
  Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization,
  Note that hospitalizations for the following reasons should not be reported as serious adverse events:

[redacted]

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

8.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent must be reported to Novartis safety within 24 hours of learning of its occurrence for the duration as specified in Appendix 3 (Section 14.3.1). Additional SAE reporting requirements, including those for the periods of screening, pre-treatment, treatment and follow-up, are also outlined in Appendix 3 (Section 14.3.1). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all

[redacted]

investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with [EU Guidance 2011/C 172/01] or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy follow up in this study will end after birth or after any adverse pregnancy outcome associated with the end of the pregnancy. In case of live birth the newborn will be followed up until 12 months of age to detect any developmental issue or abnormality that would not be seen at birth. Pregnancy outcomes must also be collected for the female partners of any males who received tisagenlecleucel in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to tisagenlecleucel infusion any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

For more information about the effects of tisagenlecleucel on reproduction please refer to the recent [Investigator's Brochure].

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator's Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

[redacted]

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 8-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

8.7 Data Monitoring Committee

Not applicable

8.8 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, and Novartis representatives from the Clinical Trial team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will perform review of safety data during their regular meetings. This review will include deaths, SAEs, AESI or any new safety signals observed in the study. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

[redacted]

9 Data collection and management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or CRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

[redacted]

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

9.3 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis.

10 Statistical methods and data analysis

Data from all participating centers will be combined.

The primary analysis will be performed when 90 patients have received tisagenlecleucel infusion and completed 6 months from study day 1 infusion or discontinued earlier. A final Clinical Study Report (CSR) will be produced once all patients complete the study.

10.1 Analysis sets

The analysis sets to be used are defined as below. The Efficacy Analysis Set (EAS) will be used as the primary efficacy analysis set. The Safety Set will be used for all the safety analysis. The Cellular Kinetic Analysis Set (CKAS) will be used for the cellular kinetic analysis.

All tables and listings will be presented by one treatment arm of tisagenlecleucel.

10.1.1 Screened Set

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

10.1.2 Enrolled Set

The enrolled set comprises all patients who are 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.

[redacted]

10.1.3 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who have received infusion of tisagenlecleucel.

10.1.4 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) includes all patients who received infusion of tisagenlecleucel and had a measurable disease at baseline.

10.1.5 Safety Set

The Safety Set includes all patients who received infusion of tisagenlecleucel. In this study the Safety Set contains the same patients as the FAS.

10.1.6 Per-Protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the EAS who are compliant with requirements of the clinical study protocol (CSP).

The protocol deviations leading to exclusion from the PPS are:

- Diagnosis of disease other than FL at baseline
- Missing or incomplete documentation of disease

In addition, patients who receive a dose less than the recommended dose 0.6×10^8 tisagenlecleucel transduced viable T cells will also be excluded.

The detailed exclusion criteria of PPS will be determined and documented in the study Statistical Analysis Plan (SAP) prior to primary analysis.

10.1.7 Cellular kinetic analysis set

The tisagenlecleucel Cellular Kinetic Analysis Set (CKAS) consists of patients in FAS 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.

[redacted].

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

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be listed by patient and/or summarized descriptively for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented (i.e., mean, median, standard deviation, minimum, maximum).

Number and percentage of patients failing prior anti-neoplastic medications/therapies will be summarized.

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

The total cells infused (cells) and total tisagenlecleucel transduced viable T cells infused (cells) will be listed and summarized using descriptive statistics. Patients will be categorized as below, within or above the prescribed dose range.

Prior and concomitant medications and significant non-drug therapies prior to and after the start of infusion will be listed by patient and summarized by the Anatomical Therapeutic Chemical (ATC) term. Transfusion during the study will be listed. In addition, whether patients have received anti-cytokine medications for the management of CRS will be summarized.

10.4 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).

10.4.1 Variable

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.

10.4.2 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.

$$H_0: p \leq 0.15 \text{ vs. } H_a: p > 0.15$$

The CRR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. P-value from binominal exact test will be provided.

The primary efficacy endpoint, CRR will be analyzed based on the data observed in the EAS.

In addition, sensitivity analysis will be performed using the local investigator response assessments instead of the IRC assessment.

10.4.3 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) (Section 14.1) for more details.

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

10.4.4 Supportive and Sensitivity analyses

The primary analysis will also be performed on the Enrolled Set and PPS using the same methodology. In addition, analysis will also be performed using all patients who satisfy all clinical eligibility criteria.

[redacted]

10.4.4.1 Subgroup analysis

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

- Age: <65 years, ≥ 65 years
- Gender: Male, Female
- Race: Asian, Black, Caucasian, Native American, Other, Pacific Islander, Unknown
- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- FLIPI at enrollment: low/intermediate, high
- FL grade: 1, 2, 3
- Number of prior lines of anti-neoplastic therapy: ≤2 lines, 3 to 4 lines, >4 lines
- PI3K inhibitor use: naïve, pretreated

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

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable because no formal hypothesis testing is planned other than for the primary objective.

10.5.2 Other secondary efficacy objectives

IRC assessment will be used in the main analysis of secondary endpoints that involve disease response.

10.5.2.1 Overall response rate (ORR)

Overall response rate is defined as the proportion of patients with a best overall disease response of CR or PR.

The ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals

10.5.2.2 Duration of response (DOR)

Duration of response (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 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

[redacted]

- New anticancer therapy (also see below for handling HSCT)
- Event documented after at least two missing tumor assessments
- 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 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). Distribution of DOR will also be estimated using the Kaplan-Meier method in which death due to reason other than FL will be censored.

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. If a patient received HSCT after a CR or PR, relapse or survival status after HSCT will be recorded on the corresponding follow-up CRFs, although data on individual disease response components (e.g. CT scan) will not be collected. In such cases, the date of relapse or death (if due to FL) after HSCT will be used for calculation of DOR as a sensitivity analysis.

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

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

10.5.2.3 Progression free survival (PFS)

Progression-free survival (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 (see below for handling of HSCT)
- Event documented after at least two missing tumor assessments
- Adequate assessments no longer available

In the main analysis of PFS, patients who proceed to HSCT after tisagenlecleucel infusion will be censored at the time of HSCT. In addition, a sensitivity analysis of PFS will be performed without censoring for HSCT.

[redacted]

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.

10.5.2.4 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.

OS will be assessed in all patients (FAS). 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.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used, unless otherwise specified. All listings and tables will be presented by one treatment arm of tisagenlecleucel.

The overall observation period will be divided into three mutually exclusive segments:

- Pre-treatment period: from day of patient's informed consent to the day before first lymphodepleting chemotherapy dose or the pre-infusion visit if the lymphodepleting chemotherapy is not given.
- Lymphodepleting period (note: this period only applies to patients who received lymphodepleting chemotherapy): from the first day of lymphodepleting chemotherapy
  - to the day before infusion of tisagenlecleucel, for patients who received infusion, or
  - to the earlier of date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy for patients who didn't receive infusion of tisagenlecleucel
- Post-infusion period: starting at day of tisagenlecleucel infusion

10.5.3.2 Adverse events (AEs)

Reporting of adverse events will be based on MedDRA and CTCAE version 4.03.

Adverse events that start or worsen after informed consent should be recorded in the patient's source documents. New or worsening adverse events prior to starting study treatment (i.e. lymphodepleting chemotherapy or the pre-infusion visit if the lymphodepleting chemotherapy is not given per Section 6.1.3) are not required to be recorded in the CRF unless it is an AE meeting criteria outlined in Section 8.1 or SAE meeting criteria outlined in Section 8.2.2. Once the patients begin lymphodepleting chemotherapy or the pre-infusion visit, all new or worsening adverse events will be recorded in the Adverse Event CRF. Summary tables for adverse events will be provided for AEs that start or worsen during the post-infusion period, i.e. the tisagenlecleucel-treatment-emergent AEs. In addition, AEs that start or worsen during the lymphodepleting period will be summarized for all patients who received lymphodepleting chemotherapy. All safety data (including those from the pre-treatment period) will be listed along with the period (as defined in Section 10.5.3.1) of the starting date of AE.

[redacted]

The incidence of tisagenlecleucel treatment-emergent adverse events (new or worsening during the post-infusion period) will be summarized by primary system organ class, preferred term, severity (based on CTCAE grades), and relation to study treatment. A patient with multiple Common Toxicity Criteria (CTC) grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of CTC grade 3 and 4 AEs will be summarized separately.

Deaths and serious adverse events will be listed by patient and tabulated by primary system organ class and preferred term.

Adverse events of special interest (AESI)

The current search criteria of AESI are based on limited experience from ongoing clinical studies without an accurate assessment of causality. AESI and the search criteria of AESI will be updated prior to reporting. AESI that occur within 8 weeks of the tisagenlecleucel infusion will be summarized by group term and preferred term.

10.5.3.3 Laboratory abnormalities

Grading of laboratory 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. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

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

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

All laboratory data will be listed with valued flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the Master Analysis Plan (MAP) and/or the Statistical Analysis Plan (SAP).

10.5.3.4 Immunogenicity

The humoral immunogenicity assay measures the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. 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.

[redacted]

[redacted]

10.5.3.5 Other safety data

Vital signs will be collected as clinically needed. Presence of detectable RCL will be tested by VSV-g at scheduled assessments in Table 7-1. All safety data will be listed.

10.5.3.6 Safety subgroup analysis

Key safety summaries for adverse events regardless of relationship to study drug by System, Organ, Class (SOC) and PT, and adverse events of special interest will be repeated on the Safety Set in the following subgroups:

- Age: <65 years, ≥ 65 years
- Gender: Male, Female
- Race: Asian, Black, Caucasian, Native American, Other, Pacific Islander, Unknown
- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- Prior HSCT therapy yes or no
- FLIPI at enrollment: low/intermediate, high

The objective of carrying out these subgroup analyses is to 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.

10.5.4 Pharmacokinetics

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.

[redacted]

Table 10-1 Noncompartmental cellular kinetic parameters

Parameter	Definition
AUC 0-28d and/or AUC 0-84d	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)
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 Month 3 and best overall response.

[redacted]

10.5.5 Electronic patient-reported outcomes

Patient Reported Outcome (PRO), such as scores of health-related quality of life questionnaires FACT-Lym, EQ-5D-3L and SF-36 will be assessed at screening, Month 3, Month 6, Month 9, Month 12, Month 18, Month 24 and at the End of Study visit. PRO data for this study will be collected by electronic devices. Summary scores will be generated by summing the item responses on the questions for each domain in accordance with the respective scoring manual provided by the developers. Descriptive statistics (e.g. mean, median and frequency) and change from baseline of the summary scores for each post baseline time-point/window of

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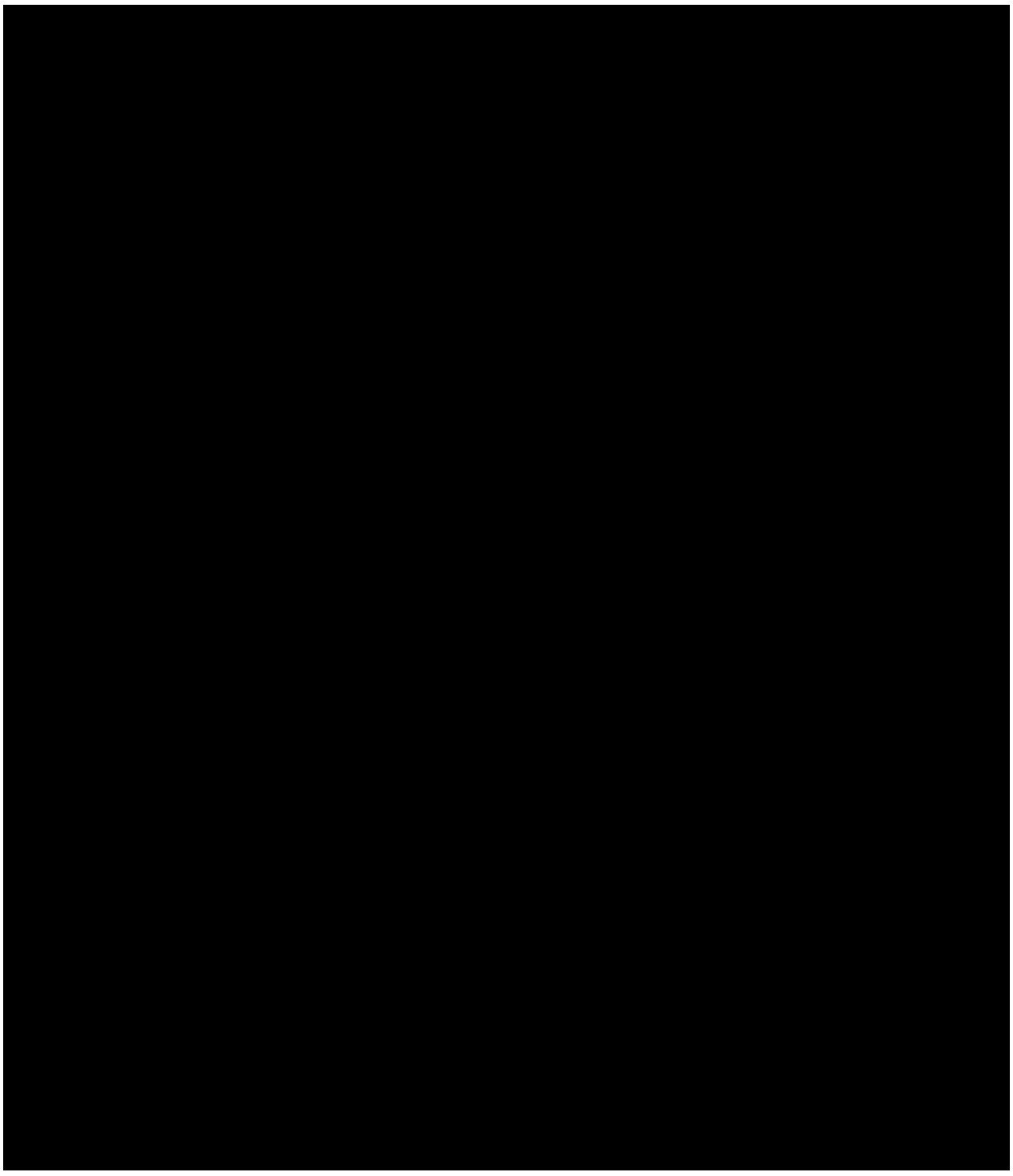
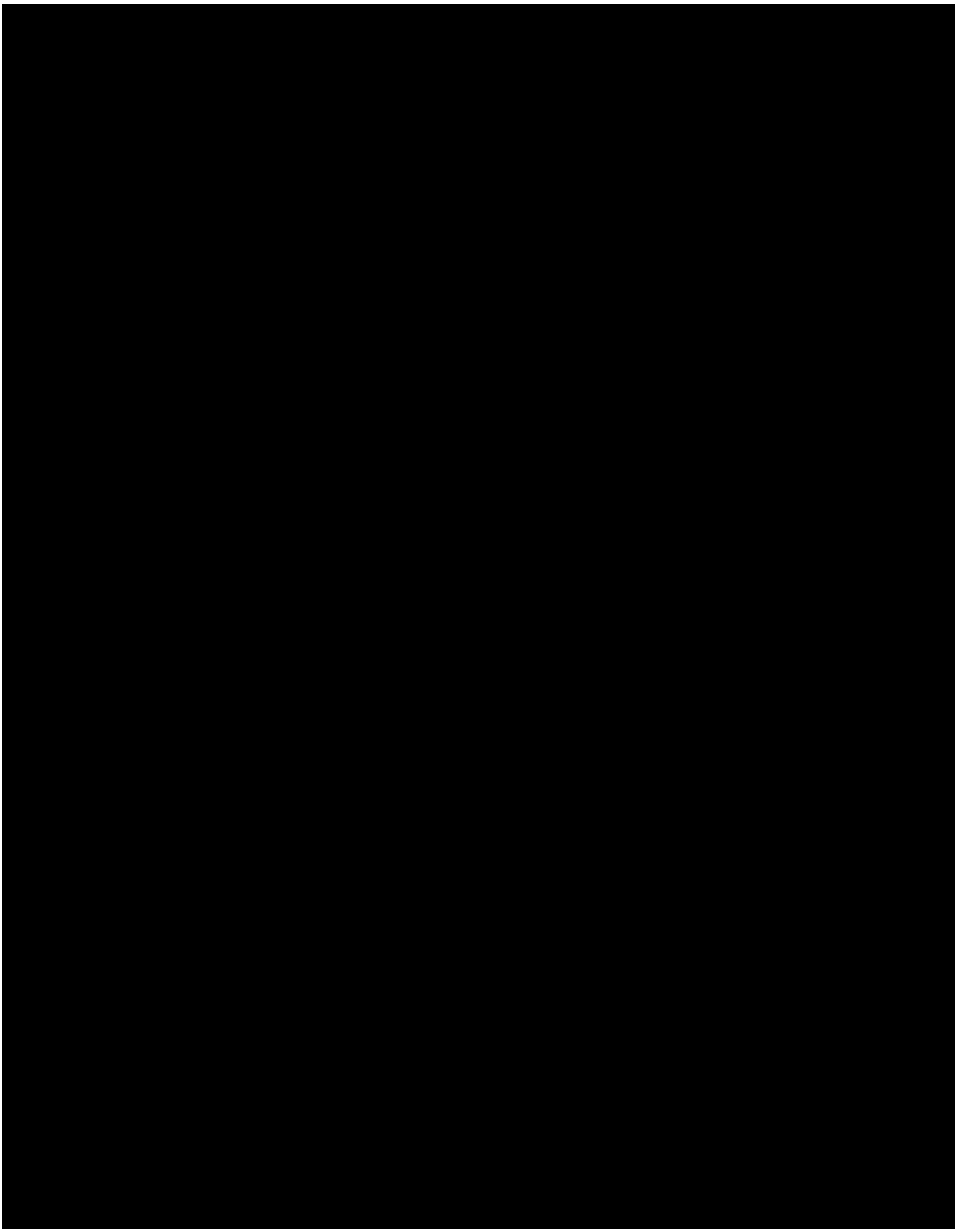
assessment will be provided based on all available data at the time of final analysis. FAS will be used for all analyses.





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10.7 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

[redacted]

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.

The operating characteristics of certain scenarios are summarized in Table 10-2 below.

Table 10-2 Scenarios for interim and final analysis

Scenario	Probability (%) to claim success at interim analysis	Probability (%) to claim success at interim or final analysis
p=0.15 (H_0)	0.19	2.35
p=0.20	3.08	24.45
p=0.25	16.31	67.06
p=0.30(H_a)	43.08	92.94
p=0.35	71.99	99.23

10.8 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.

10.9 Power for analysis of key secondary variables

Not applicable because no formal hypothesis testing is planned other than for the primary objective.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

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11.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC -approved informed consent

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

Women of child bearing potential must be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

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11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

11.6 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11.7 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

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Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.8 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.9 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.10 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: Guidelines for efficacy evaluation in non-Hodgkin lymphoma studies

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[redacted]

List of Abbreviations

BOR	Best overall response
CMR	Complete metabolic response
CR	Complete response
CT	Computed tomography
DFS	Disease-free survival
DLBCL	Diffuse large B cell lymphoma
EFS	Event-free survival
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
HSCT	Hematopoietic stem cell transplantation
LDi	Longest diameter
LSS	Lymphoma-specific survival
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin lymphoma
NMR	No metabolic response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PMD	Progressive metabolic disease
PMR	Partial metabolic response
PR	Partial response
PPD	Product of the perpendicular diameters
RD	Relapsed disease
SCT	Stem cell transplantation
SD	Stable disease
SDi	Shortest diameter
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SUV	Standard uptake value
TTCR	Time to complete response
TTP	Time to progression
TTR	Time to response
UNK	Unknown
5PS	PET five point scale

[redacted]

14.1.1 Introduction

The purpose of this document is to provide working definitions and rules to evaluate efficacy in non-Hodgkin lymphoma (NHL) studies conducted by Novartis. This document is based on the International Working Group response criteria (Cheson et al 1999), the International Harmonization Project revised response criteria (Cheson et al 2007), and the revised Consensus of the International Conference on Malignant Imaging Working Group and the Lugano Classification (Barrington et al 2014; Cheson et al 2014), and it is intended for studies of radiographically measurable disease. For studies without measurable disease, e.g., studies of consolidation of complete response, maintenance treatment, or autologous stem cell transplantation, see [Appendix A].

14.1.2 Methodologies

14.1.2.1 Computed tomography (CT)

The same method of assessment and technique should be used to characterize each identified and reported lesion throughout the study. Contrast-enhanced CT of neck, chest, abdomen and pelvis, from skull base through lesser trochanters ensuring complete coverage of the pelvis and inguinal areas, should be performed using a $\leq$ 5 mm slice thickness with a contiguous reconstruction algorithm. If a patient has a CT contrast allergy or develops it during the trial, non-contrast CT of the chest plus contrast-enhanced MRI of abdomen and pelvis are acceptable for a follow up. Chest MRI is not recommended due to respiratory artifacts.

14.1.2.2 Positron emission tomography (PET)

Studies of FDG-avid histologies require PET using the radiotracer ^{18}F-fluorodeoxyglucose (FDG) to confirm any new CR determined by CT. PET will not be required to confirm progression or relapse.

PET scans should cover the whole body from base of skull to mid-thigh. Examinations should be consistent across all time points including amount of tracer, location of injection, arm location, and scan delay. Information of height, weight, gender, administered dose, time between dose administration and imaging, and glucose level are required for each time point. PET images should be converted to SUV maps to support comparison across time points and to standardize viewing conditions.

14.1.2.3 PET-CT

Hybrid PET-CT may be used to acquire PET and CT images if CT images produced by the scanner are of diagnostic quality and include intravenous contrast. Non-diagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only images for the time point.

If diagnostic CT and PET are to be acquired on the same day, PET must be performed prior to CT with IV contrast to avoid compromising PET results.

Thus, any of the three following imagining methodologies are possible in a lymphoma study:

- PET-CT with diagnostic
- PET-CT with non-diagnostic CT and dedicated diagnostic CT

[redacted]

- Dedicated diagnostic CT and dedicated FDG PET

14.1.2.4 Magnetic resonance imaging (MRI) and PET-MRI

MRI or PET-MRI is an acceptable method of imaging if CT is contraindicated e.g., due to CT contrast allergy. If at baseline a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of the chest plus contrast-enhanced MRI of abdomen and pelvis (MRI of the chest is not recommended due to respiratory artifacts).

14.1.2.5 Five point scale (5PS)

To standardize PET interpretation, a simple reproducible scoring method called the five point scale (5PS) or the Deauville criteria has been implemented for initial staging and assessment of interim and end of treatment responses (Barrington et al 2014). The 5PS assesses the most intense uptake in a site of disease (Table 14-1).

Table 14-1 Five Point Scale (5PS)

Score	Findings
Score 1	No uptake above background
Score 2	Uptake ≤ mediastinum
Score 3*	Uptake > mediastinum, but ≤ liver
Score 4**	Uptake moderately > liver
Score 5**	Uptake markedly higher than liver and/or new lesions

* The protocol will need to define the significance of a score 3, depending on the studied disease, patient characteristics and goal of therapy
- Score 3 may be considered PET negative in low risk disease (e.g. follicular lymphoma) and where no further treatment is necessary
- Score 3 may be considered PET positive in high risk disease that is curable and aggressive (e.g. Hodgkin lymphoma, diffuse large B cell lymphoma) and in de-escalation studies

** Score 4 should be applied to uptake greater than the maximum standard uptake value (SUV) in a large region \ of normal liver and score 5 to uptake 2 times greater than the maximum SUV in the liver. PET images should be converted to SUV maps to support comparison across time points and to standardize viewing conditions.
(New) areas of uptake unlikely to be related to lymphoma will be marked as "X" (Barrington et al. 2014).

14.1.3 Definitions

14.1.3.1 Disease stage

Extent and involvement by lymphoma is described by the disease stage and is an important prognostic factor. Stage can also influence treatment decisions.

14.1.3.2 Baseline

Baseline examination should be as close as possible to the randomization/start of treatment (e.g., within 4 weeks prior to randomization/start of treatment). Longer periods may be allowed depending on the disease studied and the study design.

[redacted]

14.1.3.3 Nodal vs. extranodal lesion

A lesion can be categorized as:

- Nodal lesion (a lymph node or a nodal mass)
- Extranodal lesion (a lesion located in other organs, including spleen and liver)

14.1.3.4 Measurable disease

All anatomic measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

Throughout this document, a lesion will be called measurable if:

- It can be measured accurately in two perpendicular dimensions: longest diameter (LDi) (also known as transverse diameter), and shortest diameter (SDi), which is the longest diameter perpendicular to LDi (also known as perpendicular diameter). The LDi and SDi must be measured on the same slice.
- For a nodal lesion, LDi is greater than 15 mm, regardless of SDi
- For an extranodal lesion, if both LDi and SDi are greater than 10 mm

A lymph node not meeting the measurability criteria but with LDi greater than 15 mm (e.g. SDi cannot be measured accurately) will constitute a non-measurable nodal lesion if FDG-avid (for FDG-avid histologies).

A lymph node not meeting the measurability criteria but with LDi ranging from 11 mm to 15 mm and with SDi greater than 10 mm will be checked for relationship to disease as follows:

- If it is related to lymphoma, it will constitute a non-measurable nodal lesion (referred to as "involved node" in Cheson et al 2007)
- If not related to lymphoma and not FDG-avid, it will constitute an abnormal lymph node but not a nodal lesion for FDG-avid histologies

All lesions visible on PET but not on CT/MRI will be treated as non-measurable.

Bulky disease

Bulky disease is captured by means of the longest measurement by CT scan. The definition of bulky disease (a minimum size) should be included in the study protocol.

14.1.3.5 Assessable disease

Assessable disease refers to disease presentations that are consistent with lymphoma but are not suitable for measurement, e.g., pleural effusion, ascites, etc. Assessable disease will be followed qualitatively.

14.1.3.6 Index lesion

- Up to 6 of the largest nodes, nodal masses or other lymphomatous lesions, including extranodal lesions, measurable in two diameters (LDi and SDi)
- Should represent overall disease burden and include mediastinal and retroperitoneal disease, if involved

[redacted]

14.1.3.7 Non-index lesion

- All other lesions which are not selected as index lesions but are consistent with lymphoma
- Abnormal nodes and extranodal lesions, both measurable and non-measurable, such as cutaneous, gastrointestinal, and bone lesions, pleural or pericardial effusions, and ascites

14.1.3.8 New lesions

- Regrowth of previously resolved lesions
- A new nodal lesion > 15 mm in any axis
- A new extranodal lesion > 10 mm in any axis
- A new extranodal lesion ≤ 10 mm in any axis that is unequivocal and attributable to lymphoma
- A new assessable lesion attributable to lymphoma (e.g., ascites, pleural effusion)

14.1.4 Efficacy assessments

14.1.4.1 Eligibility

In general, patients should have at least one measurable nodal lesion (greater than 15 mm in the long axis) or at least one measurable extranodal lesion (with both LDi and SDi greater than 10 mm).

14.1.4.2 Methods of disease assessment

14.1.4.2.1 PET combined with diagnostic CT

The integration of PET into more frequently acquired CT evaluation does present a challenge to the way response is assessed in a clinical trial. The study protocol must clearly define the imaging intervals and imaging methods to be used at each imaging visit. PET scans should be performed at pre-specified times for example at randomization before treatment and at clearly defined times during and/or after the end of treatment. PET may also be acquired to confirm CT results.

The same CT imaging modality should be used at baseline and all post-baseline assessments in order to reduce the risk of false responses or progressions based on measurement error. A change in modality can be either a change in contrast use (i.e., with contrast versus without contrast) or a change in technique (e.g. from CT to MRI). Response assessments made after a change in imaging modality should be queried, and if the investigator or blinded central reviewer can provide sufficient justification, then the response can be accepted.

In order to calculate the sum of the product of the perpendicular diameters (PPD) of all index lesions, their size must be recorded throughout the study. Actual lesion measurements should be entered on the corresponding CRFs. If, during the course of the study, either of the perpendicular diameters of a lesion cannot be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g., 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by

[redacted]

neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm × 0 mm to each of the other previously measured lesions. The PPD of the current confluent mass should be used to measure response, with more than 50% increase in the PPD of the confluent mass compared with nadir of the sum of individual nodes necessary to indicate progressive disease.

If a lesion splits into several discrete lesions, the individual product of the perpendicular diameters (PPDs) of each lesion should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as an index lesion at baseline).

14.1.4.2.2 Bone marrow assessment

Bone marrow should be evaluated by biopsy or aspirate in all patients at baseline. If lymphoma involvement in bone marrow is observed at baseline, then biopsy or aspirate should be performed post-baseline to confirm radiological CR. Any deviation from this approach should be justified in the study protocol.

14.1.4.2.3 Physical examination

Skin lesions must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding CRF) and photographed including a ruler (color photography using digital camera). Response assessment of skin lesions will be performed and results will be recorded on the corresponding CRF at baseline and at the time of each radiological assessment.

14.1.4.3 Documentation of disease

For the evaluation of disease at baseline and throughout the study, the following will be recorded.

14.1.4.3.1 FDG uptake

FDG uptake in a nodal or extranodal site that is suggestive of lymphoma will be assessed using 5PS.

14.1.4.3.2 Index lesions

A minimum of one measurable index lesion and a maximum of six of the largest dominant nodal and extranodal lesions must be documented at baseline and assessed throughout the study in two dimensions. The lesions should come from different body regions representative of the patient's overall disease burden and should include mediastinal and retroperitoneal disease, if involved. Two perpendicular dimensions (LDi, SDi) must be recorded on the corresponding CRF at each assessment of a measurable lesion selected to be an index lesion.

Index nodal lesions

[redacted]

Index nodal lesions are selected from the measurable nodal lesions and should be documented at baseline and assessed throughout the study. Index nodal lesions should be from disparate regions of the body including mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Index extranodal lesions

Other organs such as breast and lung can be occasionally involved by lymphoma. Such extranodal lesions (e.g. hepatic nodules) may be included (if measurable) in the six index lesions to be assessed throughout the study. In some cases histological examination may be necessary to confirm that these lesions represent lymphoma involvement (e.g. skin lesions).

14.1.4.3.3 Non-index lesions

Non-index nodal lesions

Nodal lesions not selected as index lesions (both measurable and non-measurable) are considered as non-index lesions. Non-index lesions should be documented at baseline and assessed throughout the study. Measurements of these lesions are not required to be documented on the CRF.

Non-index extranodal lesions

Measurable extranodal lesions not selected as index lesions and all non-measurable extranodal lesions (including non-measurable but assessable disease e.g. pleural effusion) will be documented at baseline and assessed throughout the study as non-index lesions. Measurements of these lesions are not required to be documented on the CRF.

14.1.4.3.4 Spleen involvement

Splenic involvement is determined by imaging: vertical (cranial to caudal) length > 13 cm is considered as involved, and spleen length must be assessed at each imaging time point. Intrasplenic lesions should be followed as index, non-index and new extranodal lesions.

14.1.4.3.5 Liver involvement

Given variability in physical habitus and the impact of numerous medical conditions, assessment of liver size is not considered a reliable measure of hepatic involvement and therefore liver assessment is not included in the Lugano 2014 classification. Intrahepatic lesions should be followed as index, non-index and new extranodal lesions.

14.1.4.3.6 Bone marrow involvement

Lymphoma involvement in bone marrow should be documented in the CRF as “Yes” or “No” at each bone marrow biopsy and/or aspiration.

14.1.4.4 Response evaluation

The efficacy variables in the statistical analysis are based on **overall disease response**, which is a combined evaluation of response based on both radiological and clinical findings, and is determined at each post-baseline assessment. The radiological response is first obtained from CT and PET studies according to the Lugano criteria (Table 14-2) and overall disease response

[redacted]

is then determined by taking into account results of bone marrow biopsies and other clinical information (Table 14-3).

14.1.4.4.1 Radiological response

There are three separate components to radiological response, all of which should be collected on the CRF at each post-baseline assessment:

1. **CT response** based on anatomical measurements of index/non-index/new lesions and spleen length. The possible response outcomes are complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as defined in Table 14-2.
2. **PET response** based on 5PS, changes in intensity or extent of standard uptake values (SUVs) and bone marrow assessments directly from the PET scan. The possible outcomes for PET response are complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), or progressive metabolic disease (PMD) as defined in Table 14-2.
3. **Overall radiological response** combines CT response with PET response. The outcomes include CR, PR, SD, and PD. For time points when both CT and PET are available, PET response overrules CT response. Overall radiological response at a time point with CT only may also be affected by PET response obtained at a different time point.

1. Example

2. **A CT response of PR** at the same assessment as a PET response of CMR will constitute an overall radiological response of CR, and (i) a subsequent time point with CT only and CT response of PR will still constitute an overall radiological response of CR, (ii) a previous time point with CT only and CT response of PR may be upgraded to CR at the discretion of the investigator or blinded central reviewer.

Table 14-2 Radiological response assessment

		PET-based **response**	**CT-based response**
		Complete Metabolic Response (CMR) (All of the following)	**Complete Response (CR)** (All of the following)
Complete Response	**Index**	5PS† of 1, 2, or 3* with or without residual mass on 5PS	**Nodal lesion**: ≤ 15 mm in Ldi **Extranodal lesion**: Absent (0 mm x 0 mm)
	Non-index		Absent
	Spleen		Return to normal (≤ 13 cm)
	New lesions	None	None
	Bone marrow	No FDG-avid disease	Not applicable
		Partial Metabolic Response (PMR) (all of the following)	**Partial Response (PR)** (all of the following)
Partial Response	**Index**	5PS of 3*, 4 or 5 with reduced uptake compared to baseline with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. It is expected that there will be residual mass(es) present.	≥ 50% decrease from baseline in SPD across all index lesions
	Non-index		No increase
	Spleen		≥ 50% decrease from baseline in enlarged portion of spleen

[redacted]

		PET-based **response**	**CT-based response**
		Complete Metabolic Response (CMR) (All of the following)	**Complete Response (CR)** (All of the following)
			Example: *If 16 cm, then enlarged portion is 3 cm. A decrease by 2 cm gives a 66.6% decrease*
	New lesions	None	None
	Bone marrow	● Residual uptake higher than uptake in normal marrow but reduced compared with baseline ● Persistent focal changes in the marrow with nodal response	Not applicable
		No Metabolic Response (NMR) (all of the following)	**Stable Disease (SD)** (all of the following)
Stable Disease	**Index**	5PS of 3*, 4 or 5 with no significant change in FDG uptake from baseline	● <50% decrease from baseline in SPD across all index lesions ● No criteria for PD are met
	Non-index		No progression
	Spleen		No progression
	New lesions	None	None
	Bone marrow	No change in FDG uptake from baseline	Not applicable
		Progressive Metabolic Disease (PMD (At least one of the following)	**Progressive Disease (PD)** (At least one of the following)
Progressive Disease	**Index**	5PS of 3*, 4 or 5 with increased uptake compared to the visually determined nadir with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. and/or ● New FDG-avid foci consistent with lymphoma ● Consider biopsy or interval scan if etiology of new lesions uncertain	PPD Progression[#]: An individual node/lesion must be abnormal with: ● LDi > 15 mm AND ● Increase by >= 50% from PPD nadir AND ● An increase in LDi or SDi from nadir: ● ≥ 5 mm for lesions with LDi ≤ 20 mm at current assessment ● ≥ 10 mm for lesions with LDi > 20 mm at current assessment
	Non-index		Unequivocal Progression
	Spleen		● Progression (increase from baseline by >50% in enlarged portion). ***Example:*** *If 15 cm at baseline then enlarged portion is 2 cm and an increase by >1 cm would be progression* ● New splenomegaly (> 13 cm and increase by > 2 cm from normal at baseline) ● Recurrent splenomegaly (normalization followed by increase by > 2 cm from nadir reaching > 13 cm)
	New lesions		● Regrowth of previously resolved lesions

[redacted]

		PET-based **response**	**CT-based response**
		Complete Metabolic Response (CMR) (All of the following)	**Complete Response (CR)** (All of the following)
			• New node > 15 mm in any axis • New extranodal site > 10 mm in any axis • New extranodal site ≤ 10 mm in LDi, unequivocal and attributable to lymphoma • Assessable disease of any size Unequivocally attributable to Lymphoma
	Bone marrow	New/recurrent FDG-avid foci	Not applicable

Abbreviations: LDi Longest diameter; SDi Shortest diameter; PPD Product of perpendicular diameters; SPD Sum of the product of the perpendicular diameters.
* The protocol will need to define the significance of a score 3, depending on the disease under study (risk: benefit analysis), patient characteristics and goal of therapy
- Score 3: PET negative - Low risk disease and no further treatment necessary (e.g. follicular lymphoma)
- Score 3: PET positive - High risk disease that is curable and aggressive (e.g. DLBCL)
In the context of an agent associated with a flare reaction, caution must be exercised not to confuse the possible tumor flare with progressive disease. It is recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks, and if there is continued evidence of tumor progression, the date of progressive disease is the previous evaluation.
† PET 5PS 1: no uptake > background; 2: uptake ≤ mediastinum; 3: uptake > mediastinum but ≤ liver; 4: uptake moderately > liver; 5: uptake markedly > liver and/or new lesions; X: new areas of uptake unlikely to be related to lymphoma.

14.1.4.4.2 Overall disease response

Overall disease response is determined by assessing whether the combined radiological responses at each time point are appropriate, based on bone marrow biopsies and other clinical findings that may be available, such as cytology results, physical examination results of palpable lesions or skin lesions, and biopsies of lymph nodes or extra-nodal lesions (Table 14-3). The possible outcomes for overall disease response are CR, PR, SD, and PD.

For example, suppose there was lymphoma involvement in the baseline bone marrow biopsy, and the month 3 combined radiological response was CR (implying that PET-based bone marrow involvement at month 3 was negative). In that case, overall disease response could only be CR if there was a negative bone marrow biopsy otherwise overall disease response would be downgraded to PR. This is a case where the bone marrow biopsy results overrule the bone marrow findings on PET. Another example is when the combined radiological response is SD, but cytology results of a pleural effusion show lymphoma involvement: this could lead to an overall disease response of PD.

Overall disease response at each post-baseline assessment should be captured on the CRF, along with the date of response. In addition, the source of any clinical data that affected the overall disease response should be documented.

[redacted]

Table 14-3 Overall disease response

Overall radiological response	Bone marrow biopsy/aspirate	Clinical findings	Overall disease response
CR/PR/SD	Negative at baseline or negative ± 28 days from assessment	Any except new or recurrent lymphoma involvement	CR/PR/SD
CR	Positive at baseline and either positive (without new or recurrent involvement) or not done ± 28 days from assessment	Any except new or recurrent lymphoma involvement	PR
PR/SD	Positive at baseline and either positive (without new or recurrent involvement) or not done ± 28 days from assessment	Any except new or recurrent lymphoma involvement	PR/SD
PD	Any	Any	PD
Any	New or recurrent involvement	Any	PD
Any	Any	New or recurrent lymphoma involvement	PD

14.1.4.5 Efficacy analysis definitions

14.1.4.5.1 Best overall response

The best overall response (BOR) is the best overall disease response recorded from randomization/start of treatment until progressive disease or start of new anticancer therapy, whichever comes first. The definition of new anticancer therapy may need to be defined in the study protocol (e.g., high-dose chemotherapy with autologous stem cell transplantation).

A patient will have a best overall response of CR if they have CR as overall disease response for at least one of the assessments.

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

A best overall response of SD will be declared when at least one overall disease response of SD is available at least 6 weeks after randomization/start of treatment (and the patient does not qualify for CR or PR). If SD is observed before this minimum follow-up period, and the patient does not qualify for CR, PR or PD, then the best overall response would be unknown (UNK). If a different minimum follow-up period for SD is more appropriate (e.g., if first post-baseline visit is at 28 days) then this must be specified in the Study Protocol.

A patient will have a best overall response of PD if overall disease response is PD between randomization/start of treatment and the second scheduled post-baseline assessment (and the patient does not qualify for CR, PR or SD).

For example, assuming 12 weeks between assessments and a permitted variation in visit timing of ± 1 week, this would mean during the first 25 weeks after randomization/start of treatment. If PD is observed after this maximum follow-up period, and the patient does not qualify for CR,

[redacted]

PR or SD, then the best overall response would be UNK. If a different maximum follow-up period for PD is more appropriate then this must be specified in the Study Protocol.

A patient will have a best overall response of UNK if the patient does not qualify for CR, PR, SD or PD.

Overall disease response at a given assessment may be provided from different sources:

- Per Investigator: overall disease response based on local radiological assessments, using investigator choice of index lesions, measurements and assessments of lesion status and 5PS along with clinical findings
- Per Central Blinded Review, with or without blinded adjudication: based on central review of local radiological assessments, using central reviewer choice of index lesions, measurements and assessments of lesion status and 5PS, along with clinical findings

In studies that include a central blinded review, the Study Protocol should state which source will be used for the primary analysis.

Best overall response is summarized by calculating the **overall response rate (ORR)**, which is defined as the proportion of patients with a best overall response of CR or PR.

Similarly, the complete response rate is the proportion of patients with a best overall response of CR.

14.1.4.5.2 Time to event variables

Most of the time to event variables are defined in this section according to the revised International Working Group response criteria (Cheson et al 2007). Further details on dates and censoring rules are provided respectively in Section 14.1.4.5.3 and Section 14.1.4.5.4.

Overall survival

Overall survival (OS) is defined as the time from the date of randomization/start of treatment to the date of death due to any cause. If a patient is not known to have died, OS will be censored at the date of last contact.

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of randomization/start of treatment to the date of event defined as the first documented progression (overall disease response = PD) or death due to any cause. If a patient has not had an event, PFS is censored at the date of the last adequate assessment as defined in Section 14.1.4.5.3.

Time to progression

Time to progression (TTP) is defined as the time from the date of randomization/start of treatment to the date of first documented progression (overall disease response = PD) or death due to lymphoma. If a patient has not had an event, TTP is censored at the date of the last adequate assessment.

Duration of response

Duration of response (DOR) applies only to patients with best overall disease response of CR or PR. It is defined as the time from the date of the first documented overall disease response

[redacted]

of CR or PR to the date of first documented progression or death due to lymphoma. If a patient has not had an event, DOR is censored at the date of the last adequate assessment. It should be stated that this analysis might introduce a bias as it includes only responders.

Duration of complete response applies only to patients with best overall disease response of CR. It is defined as the time from the date of the first documented overall disease response of CR to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of CR is censored at the date of the last adequate assessment. Duration of CR might be calculated in addition for studies in which a reasonable number of complete responders are seen.

The analysis of DOR should only be used as a descriptive analysis. If used as an inferential comparison between treatments, clear justification must be given in the study protocol.

Time to response

Time to response (TTR) is defined as the time from the date of randomization/start of treatment to the date of first documented overall disease response of PR or CR. Depending on the study design, this analysis could be based on all patients only, or on responders only, or both of these analysis populations may be used. The choice of analysis population for TTR should be stated in the study protocol.

For analysis using all patients, TTR will be censored for patients who did not achieve a PR or CR:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause)
- At the date of the last adequate assessment otherwise

Time to complete response (TTCR) is defined similarly to TTR except using CR only instead of either PR or CR, and with this difference, the above rules and definitions for TTR also apply to TTCR.

Lymphoma specific survival

Lymphoma specific survival (LSS) is defined as the time from the date of randomization/start of treatment to the date of death documented as a result of lymphoma. If a patient has not had an event, LSS will be censored:

- at the date of last contact if the patient is not known to have died
- at the date of death if the patient died for reason other than lymphoma

Event-free survival

Event-free survival (EFS) may be appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, EFS may be considered as a sensitivity analysis for TTP. If a patient has not had an event, EFS is censored at the date of the last adequate assessment as defined in Section 14.1.4.5.3. The definition of event needs to be defined in the Study Protocol according to study design.

[redacted]

14.1.4.5.3 Definition of start and end dates for time to event variables

Assessment date

For each assessment, the assessment date is calculated as:

- the latest date of all radiological measurements (e.g. PET-CT, CT, or MRI), excluding bone marrow biopsy, if overall disease response at that assessment is CR/PR/SD/UNK
- the earliest date of all measurements (e.g. PET-CT, CT, or MRI), including bone marrow biopsy if overall disease response at that assessment is PD

Start date

For all "time to event" variables other than the duration of response variables, the date of randomization/start of treatment will be used as the start date.

For the calculation of duration of response variables the following start date should be used:

- Date of first documented response is the assessment date of the first overall disease response of CR for duration of complete response or CR/PR for duration of response

End date

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death as reported on the disposition CRF
- Date of last contact is defined as the last date the patient was known to be alive as derived from different CRF pages (see details in Section 14.1.4.5.2)
- Date of progression is the first assessment date at which the overall disease response was recorded as PD
- Date of last adequate assessment is the date of the last assessment with overall disease response of CR, PR or SD which was made before an event or a censoring reason occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate assessment plus the protocol specified time interval between assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next radiological assessment as per protocol.

Example (if protocol defined schedule of assessments is 3 months): response assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of treatment discontinuation is the last known date subject took study drug *(to be used, if applicable)*
- Date of new anti-cancer therapy is defined as the start date of first new antineoplastic therapy (including medication, radiotherapy, surgery or HSCT)

14.1.4.5.4 Censoring and sensitivity analyses

Censoring reasons

[redacted]

This section outlines the possible censoring reasons for each time to event variables. In order to summarize the various reasons for censoring, the following categories (Table 14-4) will be calculated for each time to event variable based on the information reported.

Table 14-4 Censoring reasons

Time to event variables	Possible censoring reasons
OS	• Alive • Lost to follow-up
PFS, EFS, TTP and DOR	• Ongoing without event • Lost to follow-up • Withdrew consent • Death due to reason other than lymphoma (only used for TTP and DOR) • New anti-cancer therapy added (except for EFS optional, see Table 14-5) • Event documented after two or more missing response assessments (optional, see Table 14-5) • Adequate assessment no longer available[1]
LSS	• Alive • Lost to follow-up • Death due to reason other than lymphoma

[1]Adequate assessment is defined in Section 14.14.4.5.3. This reason corresponds to any censoring reasons after two or more missing response assessments. This reason will also be used for censor in case of no baseline assessment

Event date, censoring date and sensitivity analyses

This section outlines the possible event and censoring dates for progression (Table 14-5), as well as addressing the issues of missing response assessments during the study. It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.4.5.2, and using the draft FDA guideline on endpoints (FDA 2007) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, EFS, TTP, DOR

Situation		Options for end-date (progression)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[2]	Censor
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[1]	Event Event
C1	Progression or death due to any reason after exactly one missing assessments	(1) Date of progression (or death) (2) Date of next scheduled assessment[1]	Event Event
C2	Progression or death due to any reason after two or more missing assessments	(1) Date of last adequate assessment[1] (2) Date of next scheduled assessment[1] (3) Date of progression (or death)	Censor Event Event
D	No progression	(1) Date of last adequate assessment	Censor

[redacted]

Situation		Options for end-date (progression)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Event
F	New anticancer therapy given (except for EFS, in which this is always an event)	(1) Date of last adequate assessment (2) Date of new anticancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censor Censor Event Ignored
G	Death due to reason other than lymphoma	(1) Date of last adequate assessment	Censor (only TTP and DOR)
[1] = Definitions can be found in Section 14.1.4.5.3 [2] = The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

The primary analysis and the sensitivity analyses must be specified in the Study Protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments:

The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of response assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the response due to clinical deterioration.

Situation F: New cancer therapy given (except for EFS): the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g.:

[redacted]

- By assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

Date of previous scheduled assessment (from baseline) is the date when a response assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate assessment.

The need for these types of sensitivity analyses will depend on the requirements for a specific study and disease area and have to be specified in the Study Protocol or SAP documentation.

14.1.5 Data handling and programming conventions

The following rules should be used and specified in the SAP documentation:

14.1.5.1 Calculation of 'time to event' variables

Time to event = enddate - startdate + 1 (in days)

When no post-baseline assessments are available, the date of randomization/start of treatment will be used as enddate (duration = 1 day) when time is to be censored at last assessment, i.e. time to event variables can never be negative.

14.1.5.2 Date of last contact

The date of last contact will be derived for patients alive using the latest complete date among the following:

- Assessment dates (e.g., vital signs assessment, performance status assessment, efficacy assessment, laboratory, pharmacokinetics assessment)
- Medication dates including study medication and antineoplastic therapies administered after study treatment discontinuation
- Adverse events dates
- Last known date subject alive collected on the 'Survival information' eCRF
- Randomization date

14.1.5.3 Date of new anti-cancer therapy

The date of new anti-cancer therapy is the date of the first antineoplastic therapy (including medicine, radiotherapy and surgery) reported on the post-treatment antineoplastic therapy CRF or from other sources (e.g., HSCT CRF).

14.1.5.4 Incomplete assessment dates

All investigation dates (e.g., PET-CT scan) must be completed with day, month and year. If one or more investigation 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 outlined in Section 14.1.4.5.3). If all measurement dates have no day recorded, the 1st of the month is used.

[redacted]

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.

14.1.5.5 Incomplete dates for last contact or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.1.6 References

Barrington SF, Mikhaeel NG, Kostakoglu L, et al (2014) Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32 :3048-3058.

Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244-1253.

Cheson BD, Pfistner B, Juweid ME, et al (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586.

Cheson BD, Fisher RI, Barrington SF, et al (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol 32:3059-3067.

FDA Guideline (2007) Clinical trial endpoints for the approval of cancer drugs and biologics, May 2007.

14.1.7 Appendices

Appendix A: Adaptation for use in maintenance/adjuvant settings

For study populations without measurable disease at baseline (e.g., maintenance), the event of interest is no longer progression but relapse, and the main endpoint is no longer progression-free survival but disease-free survival (see below).

Relapsed disease

Any of the following meets the definition of relapsed disease (RD):

- Any new nodal lesion > 15 mm in any axis (i.e. previously normal lymph node becoming >1.5 cm in any axis) on CT (or MRI) after baseline
- Any discrete extranodal lesion (including liver or spleen) reliably appearing on CT (or MRI) after baseline
- ≥ 50% increase in long axis from baseline of any residual lymph node or mass. A residual lymph node or mass is defined as a previously lymphoma-involved lymph node or mass (>10 mm in short axis (without any upper limit)) that was PET negative at baseline and only reliably detected by baseline CT (or MRI). Note: If a residual lymph node or mass at baseline decreases in size during treatment and becomes normal (i.e. complete disappearance of extranodal mass or ≤ 10 mm in short axis and ≤ 15 mm long axis for nodal mass), then reappearance of an extranodal lesion at the same site or increase of the

same nodal mass to > 15 mm in the long axis, will be considered RD and will be recorded as a new lesion.

- Any new bone marrow involvement
- Any new malignant effusion

Disease-free survival

Disease-free survival (DFS) is the time from date of randomization / start of treatment to the date of event defined as the first documented relapse of the disease or death due to any cause. If a patient has not had an event, DFS is censored at the date of the last adequate assessment. Similar censoring rules and reasons as the ones used for PFS can be applied.

14.2 Appendix 2: Eligibility based on serologic markers for hepatitis B and C

Test	Result				
HBsAg	+	-	-	-	-
HBcAb	Any	+	-	+	-
HBsAb	Any	-	+	+	-
HCV Ab	Any	Any	-	-	-
Eligibility	Not Eligible	Not Eligible	Eligible	Eligible	Eligible

If indeterminate results are obtained, viral DNA (hepatitis B) or RNA (hepatitis C) should be measured to confirm negative viral status.

HBsAg positive: Indicates active infection and risk for reactivation with fulminant hepatitis. These patients are not eligible for this trial.

HBcAb positive: As a standalone marker, it indicates active infection and risk for reactivation. These patients are not eligible for this trial.

HBsAb positive: As a standalone marker, it indicates successful vaccination or previous infection that has been successfully resolved if the only positive finding. These patients are eligible for this trial.

HBsAg negative, HBcAb positive, HBsAb positive: Resolved or latent infection. These patients are eligible for this trial, however, they are at risk for viral reactivation (see Kymriah label, Warnings and Precautions).

HCV Ab positive: Indicates active infection and risk for reactivation. These patients are not eligible for this trial.

All markers negative: No prior exposure or vaccination to hepatitis B and no prior exposure to Hepatitis C. Patients are eligible for this trial.

[redacted]

14.3 Appendix 3: Tisagenlecleucel modified data reporting – Treatment and Follow-up Phase

This guidance is used to determine whether or not an AE, SAE, concomitant medication, or laboratory result has to be recorded in the CRF during the relevant study period. Before using this guidance, the investigator should determine whether or not an adverse event is serious using the criteria found in the protocol section 8, and then use the applicable row of this guidance to determine whether or not that event is to be recorded in the CRF.

14.3.1 Adverse event (AE) and serious adverse event (SAE) reporting

	Screening and Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment and Follow-up Period** (Starting from LD chemo/pre-infusion visit)	**Post-treatment Period** (After Month 12, through End of Study and under LTFU protocol CTL019A2205B for 15 years post-infusion)
		Through Month 12 Visit	**After Month 12 Visit**
Non-serious Adverse Events (AE)	Modified: All infections All laboratory abnormalities deemed clinically significant by the investigator All clinical AEs grade ≥ 3 All AEs related to a study procedure All AEs leading to study discontinuation	All, including all laboratory abnormalities deemed clinically significant by the investigator	Modified –Whether serious or non-serious, report following: Events leading to death Related to a study procedure Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria: Lead to significant disability or hospitalization OR Need surgical or other intervention New incidence or exacerbation of a pre-existing neurologic disorder (tisagenlecleucel patients only) New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder New incidence of other hematologic disorder Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy Positive RCL test result (tisagenlecleucel patients only) Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene (tisagenlecleucel patients only) New malignancy (T-cell & non T-cell), other than the primary malignancy Progressive multifocal leucoencephalopathy (PML) Hepatitis B reactivation
Serious Adverse Events (SAE)	Modified: All events leading to death All events related to a study procedure Any AE reportable for this study period that also meets criteria for serious All pulmonary or cardiac abnormalities All infections Any substantial change in the status of the patient that precludes the patient from proceeding to study treatment (e.g. GVHD, rapid progression of malignancy, marked decline in performance status) Any other substantial change in the status of the patient that the investigator deems may have a potential impact on the patients during lymphodepletion and tisagenlecleucel treatment	All	

[redacted]

14.3.2 Concomitant medication and laboratory reporting

	Screening and Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment and Follow-up Period** (Starting from LD chemo/pre-infusion visit, through Month 12)		**Post-treatment Period** (After Month 12)
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**	**Inpatient/ICU OR Outpatient**
Concomitant medications	Modified: **Drugs:** Record **all** of the following medications: Anticytokine therapies (e.g. tocilizumab, or other) Corticosteroids (including prophylactically for blood product administrations, physiologic replacement doses, high or stress doses, etc.) Anti-seizure medications Allopurinol, or non-allopurinol alternatives Rasburicase Immunoglobulin therapy Any medication given therapeutically for an SAE Vasopressors and cardiac inotropic agents (see below) Narcotics and sedatives (see below) Antineoplastic therapies (e.g. lymphodepleting chemotherapy) Related to an AE or SAE defined as reportable for this period **Vasopressors and cardiac inotropic agents:** For dose, record only maximum daily rate (e.g. µg/kg/hr, mg/hr, etc.) **Narcotics and sedatives:** For dose, record only total daily dose **Blood products (e.g. red cells, platelets, FFP, cryoprecipitate):** Record all blood products, including prophylaxis **Electrolyte & vitamin replacement:** Record all electrolyte replacement if given for a clinically significant electrolyte disturbance and list these as an adverse event (AE). Do **not** record prophylactic use of electrolyte or vitamin replacements Do **not** record total parenteral nutrition (TPN) on concomitant medication CRF **Fluids:** Do **not** record fluid boluses and maintenance fluids **Antibiotics:**		All	Modified: Related to an AE or SAE defined as reportable for this period Mutagenic agents (including cytotoxic drugs) Radiation & antineoplastic therapy (including SCT) Immunoglobulin therapy Immunosuppressive agents (including dose of steroids higher than physiologic replacement therapy doses of steroids (< 12 mg/m2/day hydrocortisone or equivalent) Investigational therapy

[redacted]

	Screening and Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment and Follow-up Period** (Starting from LD chemo/pre-infusion visit, through Month 12)		**Post-treatment Period** (After Month 12)
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**	**Inpatient/ICU OR Outpatient**
	Record all antibiotics starting from day of infusion, even if given prophylactically			
Laboratory data	Modified: Record **all** scheduled labs (per Visit Evaluation Schedule) Record **all** results (scheduled or unscheduled) for: LDH, Uric acid, CRP, Ferritin, and fibrinogen (related to CRS/TLS/MAS) Record all other laboratory values if they are ≥ Grade 3 For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled) For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia) Laboratory abnormalities that are not clinically significant and treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)		All	Modified: Record **all** scheduled labs (per Visit Evaluation Schedule) Record **all** results (scheduled or unscheduled) for: LDH, Uric acid, CRP, Ferritin, and fibrinogen (related to CRS/TLS/MAS) Record all other laboratory values if they are ≥ Grade 3 For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled) For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia) Laboratory abnormalities that are treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)

[redacted]

14.4 Appendix 4: Liver event and Laboratory trigger Definitions and Follow-up Requirements

14.4.1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

[redacted]

14.4.2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study treatment immediately (if applicable) Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT, until resolution (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study treatment immediately (if applicable) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study treatment immediately (if applicable) Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for more than 2 weeks, discontinue the study treatment (if applicable) Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	Discontinue the study treatment immediately (if applicable) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks

Criteria	Actions required	Follow-up monitoring
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately (if applicable) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study treatment immediately (if applicable) Hospitalize the patient Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study treatment interruption or discontinuation (if applicable) Hospitalization if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

[redacted]

14.5 Appendix 5: Specific Renal Alert Criteria and Actions and Event Follow-up

14.5.1 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	Consider causes and possible interventions Follow up within 2-5 days
Serum creatinine increase ≥50 % [+] OR if <18 years old, eGFR ≤35 mL/min/1.73 m^2	Consider causes and possible interventions Repeat assessment within 24-48 hours if possible Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR (Spot) urinary protein-creatinine ratio (PCR) ≥ 1g/g (or mg/ mmoL equivalent as converted by the measuring laboratory)	Consider causes and possible interventions Assess serum albumin & serum total protein Repeat assessment to confirm Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥3+ on urine dipstick	Assess & document Repeat assessment to confirm Distinguish hemoglobinuria from hematuria Urine sediment microscopy Assess serum creatinine Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation Consider bleeding disorder

[+]Corresponds to KDIGO criteria for Acute Kidney Injury

[redacted]

Table 14-6 Follow-up of renal events

Assess, document and record in the appropriate CRF

- Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells
- Blood pressure and body weight
- Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid
- Urine output

Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF.

Monitor patient regularly (frequency at investigator's discretion) until:

- Event resolution: serum creatinine within 10% of baseline or PCR <1 g/g or albumin-creatinine ratio <300 mg/g)

or

- Event stabilization: serum creatinine level with ± 10% variability over last 6 months or PCR stabilization at a new level with ± 50% variability over last 6 months

Analysis of urine markers in samples collected over the course of the renal event

[redacted]