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CTL019, tisagenlecleucel, Kymriah™

CCTL019C2202 / NCT03610724

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

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List of abbreviations

5PS	PET five point scale
ABC	activated B-cell
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	anatomical therapeutic chemical
ATG	anti-thymocyte globulin
AV	atrioventricular
B-AL	B-cell leukemia
BCLU	B-cell lymphoma, unclassifiable
b.i.d.	bis in die/twice a day
BL	Burkitt lymphoma
BM	bone marrow
BMI	body mass index
BOR	best overall response
BSA	bovine serum albumin
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAPD	Cornell Assessment of Pediatric Delirium
CAR	chimeric antigen receptor
CCG	CRF completion guidelines
CFR	code of federal regulations
CGD	chronic granulomatous disease
CI	confidence interval
CKAS	cellular kinetic analysis set
CLL	chronic lymphoblastic leukemia
CMO	contract manufacturing organizations
CMO&PS	chief medical office and patient safety
CMR	complete metabolic response
CMV	cytomegalovirus
CNS	central nervous system
COA	clinical outcome assessment
COG	children’s oncology group
CR	complete remission

[redacted]

CRA	clinical resource associate
CRES	CAR-T cell related encephalopathy syndrome
CRi	complete remission with incomplete blood count
CRF	case report/record form (paper or electronic)
CRO	contract research organization
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CSR	clinical study report
CT	computerized tomography
CTC	common terminology criteria
CTCAE	common terminology criteria for adverse events
ctDNA	circulating tumor DNA
CV	coefficient of variation
CYVE	high-dose cytarabine and etoposide
DFS	disease-free survival
DILI	drug-induced liver injury
DIN	drug induced nephrotoxicity
DLBCL	diffuse large b-cell lymphoma
DLI	donor lymphocyte infusions
DMC	Data monitoring committee
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
EAS	efficacy analysis set
EBV	Epstein-bar virus
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiography
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
EFS	event-free-survival
EMA	European medicines agency
EOS	end of study
eSource	electronic source
EU	Europe
FAB	French-American-British
FACT	Foundation for the Accreditation of Cellular Therapy
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose

[redacted]

FFPE	formalin-fixed, paraffin-embedded
FL	follicular lymphoma
FNA	fine needle aspiration
FPFV	first patient first visit
GCB	germinal-center B-cell-like
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte macrophage-colony stimulating factor
GVHD	graft-versus-host disease
GTD	greatest transverse diameter
GZL	gray zone lymphoma
HbcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HGBL	high-grade B-cell lymphoma
HIV	human immunodeficiency virus
HLA	histocompatibility antigens
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplant
HSV	herpes simplex virus
IB	investigator's brochure
ICANS	Immune effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune effector Cell-associated Encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation
ICN	ifosfamide, carboplatin and novantrone
ICU	intensive care unit
ID	identification
IEC	independent ethics committee
IFN-γ	Interferon gamma
IGH	immunoglobulin heavy
IL	interleukin
IN	investigator notification
IND	investigational new drug
INR	International Normalized Ratio
IPNHLRC	International Pediatric non-Hodgkin Lymphoma Response Criteria
IRB	institutional review board
IRT	interactive response technology
IT	intrathecal therapy
ITP	thrombocytopenic purpura
IUD	intrauterine device

[redacted]

IUS	intrauterine system
i.v./IV	Intravenous
IVIG	Intravenous immunoglobulin
JACIE	Joint Accreditation Committee of the ISCT and the EBMT
JC	John Cunningham
KM	Kaplan-Meier
LD	lymphodepleting
LDi	longest transverse diameter of a lesion
LDH	lactate dehydrogenase
LFT	liver function test
LISA	lentivirus insertion site analysis
LLOQ	lower limit of quantification
LMB	Lymphome Malins de Burkitt
LSS	lymphoma specific survival
LTFU	long-term follow-up
LTR	long terminal repeats
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MCL	mantle cell lymphoma
MedDRA	medical dictionary for regulatory activities
mg	milligram(s)
MHC	major histocompatibility complex
MI	myocardial infarction
MMc	maternal microchimerism
MR	minor response
MRA	magnetic resonance angiogram
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI	National Cancer Institute
NHL	non-Hodgkin’s lymphoma
NMR	no metabolic response
NR	no response
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction/protein-creatinine ratio
PD	progressive disease/pharmacodynamics
PE	physical exam
PET	positron emission tomography
PFS	progression free survival
PIP	pediatric investigation plan

[redacted]

PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
PMD	progressive metabolic disease
PMR	partial metabolic response
PPD	product of perpendicular diameters
PR	partial response
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorders
QC	quality control
Q.D.	once a day
QMS	quality management system
qPCR	quantitative polymerase chain reaction
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
r/r	relapse/refractory
RAP	report and analysis plan
RBC	red blood cell(s)
RCL	replication competent lentivirus
RD	relapsed disease
RFS	relapse free survival
RNA	ribonucleic acid
R Value	ALT/ALP x ULN
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee
SCID-X1	X-linked severe combined immunodeficiency
sCR	serum creatinine
SCT	stem cell transplant
SD	standard deviation
SDi	shortest axis perpendicular to LDi
SOP	standard operating procedure
SPD	sum of the product of the perpendicular diameters for multiple lesions
SUSAR	suspected unexpected serious adverse reactions
SUV	standard uptake value
TBIL	total bilirubin
TCR	T-cell receptors
TLS	tumor lysis syndrome
TNC	total nucleated cell
TNF	tumor necrosis factor
[redacted]	[redacted]
TTCR	time to complete response
TTP	time to progression
TTR	time to response
ULN	upper limit of normal

[redacted]

ULQ	upper limit of quantification
UNK	unknown
US	United States
UTI	urinary tract infection
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 cell
WHO	World Health Organization
WoC	withdrawal of consent

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (eg: any background therapy)
Baseline efficacy assessment	If multiple assessments are performed prior to infusion/randomization then the one closest temporally prior to infusion will serve as baseline assessment.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Dosage	Dose of the study treatment given to the subject in a time unit
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject infused or at a later point in time as defined by the protocol.
Final Enrollment	Point/time of subject entry into the study when the following have been confirmed: A. ICF signed B. Local subject eligibility completed C. Leukapheresis material reviewed and accepted for manufacturing
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of each study treatment package
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (eg: Screening, Treatment, and Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.

[redacted]

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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures.
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent is defined as when a subject 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 study related contact, and does not allow analysis of already collected biologic material.

[redacted]

Amendment 1

Amendment rationale

At the time of this protocol amendment (January 2020), 24 sites have been initiated, and 8 patients have been enrolled in study.

The protocol is being amended to accommodate the below listed key changes, to align with the approved Pediatric Investigation Plan (PIP) modification and to align with the tisagenlecleucel program language updates and corrections and clarifications to statements based on feedback received from the sites/ethics committees.

This protocol amendment aims to make the following key changes:

1. Update of inclusion criteria to allow patients between 18 and 25 years of age to be considered for study as B-NHL in the adolescent and young adult population is believed to be more similar to that seen in pediatric patients. Pediatric patients with Burkitt lymphoma have the same biological features and clinical behavior to at least or equal to 25 years of age (Bouska et al 2017); the expression of cytogenetic and molecular markers in DLBCL that are associated with a poorer prognosis most strongly increases between 24 and 36 years of age (Klapper et al 2012); and the immunophenotype of PMBCL in young adult patients showed a similar pattern that seen in childhood (Oschilles et al 2011).
2. Update of inclusion criteria to allow Burkitt leukemia to be considered for study. Burkitt lymphoma and Burkitt leukemia have identical cytogenetic aberrations, surface markers and molecular genetics. These two subsets are treated under the same chemotherapy regimen and share the same prognosis (Patte et al 2001, Cairo et al 2007).
3. Addition of a Data Monitoring Committee (DMC) for safety monitoring based on feedback from European Medicines Agency (EMA).
4. Updates were made to the CRS management algorithm (removal of high dose corticosteroids for high grade CRS) to align with the [Investigator's Brochure] and current practices within the CAR-T cell community.
5. New neurotoxicity grading based on immune effector cell-associated neurotoxicity syndrome (ICANS).
6. Added new allowance for prior history of Hepatitis B or C as long as lack of active disease is established.
7. Removal of ALC and absolute CD3+ T cell requirements from the inclusion criteria. These count requirements are needed only prior to leukapheresis, and many patients enrolling on the trial will have historical leukapheresis products.
8. To further ensure patient safety, added pre-infusion criteria 11 to ensure women of child-bearing potential have pregnancy testing.
9. For patients with poor clinical condition and/or low body weight, PK and immunogenicity related samples should only be collected if additional blood sampling does not result in an important concern such as interference with the medical management or clinical risk for the patient.

[redacted]

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the informed consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Changes to Protocol

1. List of abbreviations: Updated with new terms.
2. Protocol Summary: Updated to align with changes made in other sections of protocol.
3. Figure 1-1: Footnote updated to reflect newer references. CTL019 Investigator's Brochure updated to Tisagenlecleucel Investigator's Brochure here and throughout protocol.
4. Section 3: Study design updated to align with approved Pediatric Investigation Plan (PIP) modification, allow for more than one bag of cells to be administered if needed, describe staggered infusions of Burkitt leukemia patients and clarify End of Study.
5. Section 4.1.1: Reference to medications restrictions (Section 6.2.2) added.
6. Section 4.2: Clarification of dosing provided.
7. Section 4.5.1.1: Updated Cytokine Release Syndrome (CRS)/Macrophage Activation Syndrome (MAS) to align with CTL019 program language for management and grading
   a. Table 4-1: Neurologic symptoms removed
   b. Table 4-2: Table added with updated CRS grading
8. Section 4.5.1.2: Updated neurological adverse reactions to align with CTL019 program language for grading and assessment
   a. Table 4-3: Table added with ICANS Grading
   b. Table 4-4: Table added with Encephalopathy Assessment
   c. Table 4-5: Table added with ICE Score
9. Section 4.5.1.5.1: Updated Viral reactivation to align with CTL019 program language.
10. Section 4.5.1.7: Removed PML from Prolonged depletion of normal B cell and hypo- or agammaglobulinemia to align with CTL019 program language
11. Section 4.5.2.2: Investigational Product Handling Manual updated to Novartis Product Handling Manual for Clinical Trials: CAR-T Product. Updated throughout protocol.
12. Section 4.5.2.3: Updated New or secondary malignancies to align with CTL019 program language

[redacted]

14. Section 4.5.2.6: Removed Neurological events (late) section as this information is covered in 4.5.1.2. Subsequent section numbers updated accordingly.
15. Section 4.5.2.7: Added Transmission of infectious agents to align with CTL019 program language.

[redacted]

16. Section 4.5.2.8: Added Decrease in cell viability due to inappropriate handling of the product to align with CTL019 program language.
17. Section 4.5.3.1: Removed Maternal CD 19 CAR T cells details in this section to align with CTL019 program language
18. Section 5: Updated Population to align with PIP modification.
19. Section 5.1:
    a. Inclusion criteria 2: Updated to allow for inclusion of patients with Burkitt leukemia.
    b. Inclusion criteria 3: Updated to allow for inclusion of patients ≤ 25 years old.
    c. Inclusion criteria 5: Updated to allow for inclusion of Burkitt leukemia patients who have only bone marrow involvement.
    d. Inclusion criteria 7: Removed ALC and absolute CD3+ T cell requirements.
20. Section 5.2:
    a. Exclusion criteria 6: Infection language updated to align with CTL019 program language.
    b. Exclusion criteria 7: Removed 'or prior' and changed the Appendix 2 to Appendix 3 to align with CTL019 program language.
    c. Exclusion criteria 13: Updated to align with CTL019 program language.
    d. Exclusion criteria 17: Updated to align with CTL019 program language.
    e. Exclusion criteria 18: Updated to align with CTL019 program language.
21. Section 6.1.2: Removal of 'single' and 'infusion' to clarify dosing.
22. Section 6.1.3:
    a. Clarified pre-infusion criteria 8 as patients are likely to have some mild toxicities following lymphodepletion.
    b. Added pre-infusion criteria 11 to ensure women of child-bearing potential have pregnancy testing.
23. Section 6.1.4:
    a. Tumor lysis syndrome (TLS): other suggested lab testing added. Reference to management Section 6.6.2.4 added.
    b. Cytokine Release Syndrome: updated to align with CTL019 program language.
24. Section 6.1.5.1: Reference to medications restrictions (Section 6.2.2) added.
25. Section 6.1.6: Clarified timing of tisagenlecleucel administration.
26. Section 6.2.1: Added CTL019 program language to describe collection of concomitant therapies.
27. Section 6.2.2:
    a. Medication restrictions prior to leukapheresis updated to allow for steroids and low dose chemotherapy >72 hours prior to leukapheresis to stabilize disease.
    b. Medication restrictions prior to and post tisagenlecleucel infusion updated to provide wash-out of >8 weeks for cranial radiation.
    c. Removed ‘Investigational Leukapheresis, Cryopreservation and Scheduling Manual’ and updated to [Novartis Leukapheresis, Cryopreservation, and Scheduling Manual for Clinical Trials: CAR-T Product]. This update was also made throughout remainder of protocol.

[redacted]

d. Removed 'Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours prior to tisagenlecleucel infusion and long acting G-CSF should not be given within 10 days prior to tisagenlecleucel infusion.

28. Section 6.6.2.1: Added language to ensure timely access to additional doses of tocilizumab and reference to Tocilizumab USPI added.
    a. Added wording for additional assessments and/ or hospitalization if requested by HA or EC/IRB
    b. Table 6-1 – Table 6-2: Updated to align to the CTL019 program for CRS management and grading. Table entitled 'Definition of high dose vasopressors'
29. Section 6.6.2.2: Neurological AE section updated to align to the CTL019 program language
30. Section 6.6.2.7: Removed language for neurologist consult in the context of progressive multifocal leukoencephalopathy (PML) since PML is not an identified risk.
31. Section 6.7: Removed reference to Appendix 2 and throughout the remainder of the document since this Appendix is now removed.
32. Section 6.7.1: Clarified timing of tisagenlecleucel administration. Tisagenlecleucel disposal and destruction language added to align with CTL019 program template.
33. Table 8-1: Assessment Schedule:
    a. Screening window changed from 'W-16 to W-12' to 'W-16 to W-1'
    b. Removed D2, D7, D14 and D21 heights.
    c. Flow cytometry leukapheresis changed to Local from Central.
    d. Local cytokine testing removed.
    e. Removed monthly urine pregnancy tests and clarified need for pre-lymphodepletion serum testing.
    f. Removed urinalysis on day of infusion.
    g. Removed CMV and EBV testing.
    h. Frequency of bone marrow aspirate or biopsy added for Burkitt leukemia and updated for patients with bone marrow involvement.
    i. Added IVIG, ICANS grading and ICE Score.
    j. Updated schedule for Cytokines.
    [redacted]
    l. Screening Tisagenlecleucel PK on bone marrow and CSF removed. PK by flow cytometry added to assessment schedule. Footnote added to table for clarification on exempted patients.
    m. Addition of EOS column.
    n. Clarification of Month 12 requirement for Tisagenlecleucel PK flow cytometry (peripheral blood).
34. Section 8.1: Clarified acceptable windows for Standard of Care testing to be used as part of Screening. Other updates made for accuracy.
35. Section 8.1.2: Clarified that leukapheresis material must be collected at a Novartis certified leukapheresis center.

[redacted]

36. Section 8.1.3: Added 'In such cases, a rescreening CRF must be filled in to ensure the subject's original ID can be linked to the subject's new ID.'
37. Table 8-2: Clarified lesions being assessed with color photography during treatment/follow-up as being skin lesions. Table also updated with wording for Burkitt leukemia
38. Section 8.3.2: Clarified timing of bone marrow and CSF assessments.
39. Table 8-3:
    a. Removed reference to Appendix 1 as this is an error.
    b. Weight and height assessments clarified.
40. Table 8-4: Updated with most recent version of Lansky Scale.
41. Table 8-5: Removal of labs that are no longer required or were repeated within table. Added flow cytometry on leukapheresis product.
42. Section 8.4.4.1: Updated ECG section to align with CTL019 program language.
43. Section 8.5.1: Clarification provided regarding subjects exempt from PK and immunogenicity sampling.
44. Section 8.5.1.2: Added 'For patients with poor clinical condition and/or low body weight, blood samples for PK and immunogenicity analysis should only be collected if an additional blood sampling does not result in an important concern such as interference with the medical management or clinical risk for the patient'
    a. Table 8-7: Updated tables to limit volumes drawn, remove screening samples, and clarify sampling for subjects ≤15kg.
45. Table 8-16: Updated window for Enrollment in Peripheral blood for serum cytokine analyses to be consistent with rest of protocol. [redacted]
46. Section 9.1.1: Manufacturing failure listed as reason for Study Discontinuation. Details of how manufacturing failure will be handled added.
47. Section 9.1.2: Updated to include lost to follow-up as a reason for discontinuation.
48. Section 9.1.5: Clarified possible reasons for Early study termination by sponsor.
49. Section 9.2: Removed death as reason for EOS assessment(s) to be performed. Removed details of assessments to be performed on long-term follow-up study. Clarified that subjects who withdraw consent would be offered long-term follow-up study entry.
50. Section 10.1.1: Criteria for Adverse Events version updated to 5.0. Update made throughout the remainder of protocol. Updates made to align with CTL019 program language.
51. Section 10.1.2: Updates made to include collection of specific instances of disease progression as SAEs as well as other updates to align with CTL019 program language.
52. Section 10.1.3: Appendix number updated from 'Appendix 3' to 'Appendix 4'
53. Section 10.1.5: Appendix number updated from 'Appendix 3' to 'Appendix 4'
54. Section 10.1.6: Pregnancy reporting updated to provide guidance for follow-up of live births.

[redacted]

56. Section 10.2.4: DMC to monitor safety is added to the study.
57. Section 12.1.4: Clarified the definition of the Efficacy Analysis Set to ensure it aligns with primary and secondary objectives.
58. Section 12.4.4.1: Definition of age subgroups updated.
59. Section 12.5.1.1 - Section 12.5.1.4: Removal of "Event documented after at least two missing tumor assessments" as censoring reason in order to capture all events and to align at a program level, based on feedback from Norwegian Health Authority.
60. Section 12.5.2.3: Clarification of wording regarding safety post tisagenlecleucel infusion.
61. Section 12.8.1: Added the sample size requirement for subjects <18 years for subgroup analysis of the primary endpoint.
62. Section 15: References updated.
63. Section 16.1.3.2: Screening requirements added for subjects with diagnosis of Burkitt leukemia.
64. Section 16.1.3.5: Measurable disease defined for subjects with Burkitt leukemia.
65. Section 16.1.4.2.2: Updated to reflect inclusion of Burkitt leukemia patients and need for more frequent bone marrow assessments in these subjects.
66. Section 16.1.4.3.4: Spleen involvement section was updated to align with definitions of Response Criteria (Table 16-3).
67. Previous named Section 16.2 Appendix 2: Non-Mobilized Leukapheresis and Cryopreservation Recommendations and Required Product Targets removed as section duplicates information in Novartis Leukapheresis, Cryopreservation, and Scheduling Manual for Clinical Trials: CAR-T Product. Subsequent Section/Appendix numbers and Table numbers updated accordingly. References to effected Section/Appendix numbers and Tables updated throughout the protocol.
68. Section 16.2: Updated with new eligibility algorithms for Hepatitis B and C.
69. Table 16-7 and Table 16-8: Updated to align with CTL019 program template.
70. Table 16-13: In text table numbers updated and reference added.

Protocol Summary

Protocol number	CCTL019C2202
Full Title	A Phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in pediatric subjects with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL)
Brief title	A Phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in children and adolescents with non-Hodgkin lymphoma (NHL)
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Biological/Vaccine
Study type	Interventional
Purpose and rationale	The purpose of the study is to assess the efficacy and safety of tisagenlecleucel in children and adolescents with r/r B-cell NHL. For pediatric subjects who have recurrent or refractory (r/r) B-cell NHL, survival rates are dismal, only ~20-50% subjects are alive at 2 years with overall response rate (ORR) of 20-30% after conventional salvage chemotherapy.
Primary Objective(s)	Evaluate the efficacy of tisagenlecleucel therapy as measured by ORR and determined by local investigator assessments in subjects with aggressive r/r B-cell NHL ([redacted]
Secondary Objectives	• Evaluate the duration of response (DOR) in subjects with aggressive r/r B-cell NHL • Evaluate event free survival (EFS) in subjects with aggressive r/r B-cell NHL • Evaluate relapse free survival (RFS) in subjects with aggressive r/r B-cell NHL • Evaluate progression free survival (PFS) in subjects with aggressive r/r B-cell NHL • Evaluate overall survival (OS) in subjects with aggressive r/r B-cell NHL • Evaluate the safety of tisagenlecleucel therapy • Characterize the in vivo cellular kinetics (levels, expansion, persistence) of tisagenlecleucel cells into target tissues (blood, bone marrow, lymph nodes, cerebral spinal fluid and other tissues if available), as measured by qPCR in relation to safety and efficacy • Characterize the presence of pre-existing and treatment induced immunogenicity and impact on cellular kinetics and response • Assess the proportion of subjects who proceed to transplant post-tisagenlecleucel therapy until end of study (EOS) • Retrospective assessment of potential CRS predictive models considering also data from other CTL019 trials
Study design	A Phase II, single arm, multicenter, open label study to determine the safety and efficacy of tisagenlecleucel in pediatric subjects less than 18 years of age (and young adults aged equal or less than 25 years) and weighing at least 6 kg with CD19+ r/r mature B-cell NHL, who have relapsed after one or more prior therapies (can include allogeneic and autologous HSCT) or have primary refractory disease (i.e. have not achieved a CR or PR after first line therapy), with the following sequential phases: Consent, Screening, Pre-treatment, Treatment

[redacted]

	and Follow-up. Efficacy will be assessed until relapse, progression, death, lost to follow up, withdrawal of consent or EOS; safety will be monitored throughout the duration of the study. After EOS, subjects will be asked to continue in a post-study long-term follow-up (LTFU) under a separate destination protocol [CCTL019A2205B], for up to 15 years post-infusion.
Population	The target patient population participating in the study will include male and female pediatric patients less than 18 years of age (and young adults aged equal or less than 25 years) and weighing at least 6 kg with CD19+ r/r mature B-cell NHL, including broad histological aggressive subtypes based on the World Health Organization (WHO) classification (Swerdlow et al 2016), such as Burkitt lymphoma/Burkitt leukemia (BL), diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), gray zone lymphoma (GZL), as well as the indolent subtype of follicular lymphoma (FL) who have relapsed after one or more prior therapies or are primary refractory (have not achieved a complete response (CR) or partial response (PR) after the first line of therapy). Patients who have progressed after prior hematopoietic stem cell transplant (HSCT) are allowed to participate in the study. It is planned to enroll approximately 35 pediatric patients with an aim to have 26 infused and evaluable patients with aggressive subtypes available for the primary analysis. In addition, pediatric patients with follicular lymphoma will be enrolled until the 26 patients with aggressive subtypes have been infused and are available for primary analysis.
Inclusion criteria	Patients eligible for inclusion in this study must meet **all** of the following criteria: 1. Signed informed consent and assent forms if applicable must be obtained prior to participation in the study 2. Histologically confirmed (local evaluation) mature B-cell non-Hodgkin lymphoma (B-cell NHL) including the following subtypes; Burkitt lymphoma/Burkitt leukemia (BL), diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), gray zone lymphoma (GZL), and follicular lymphoma (FL) **Note:** Patients with B-cell NHL associated with Nijmegen breakage syndrome will be allowed. a. Sufficient formalin-fixed, paraffin-embedded (FFPE) tumor sample must be available for correlative analyses. A recent tumor sample obtained for the purpose of the study must be submitted, however if not clinically feasible, an archival tumor biopsy from the most recent relapse may be submitted instead. Excisional biopsies should be submitted wherever possible; in cases where this is not possible a core needle biopsy is allowed. Fine needle aspiration (FNA) is not suitable. 3. Patients ≤25 years of age and weighing at least 6 kg at the time of screening 4. Patients who have relapsed after one or more prior therapies (can include allogeneic and autologous hematopoietic stem cell transplant) or are primary refractory (have not achieved a CR or PR after the first line of therapy) 5. Measurable disease by radiological criteria in all patients at the time of screening. Patients with Burkitt leukemia who don't meet radiological criteria must have bone marrow involvement of >25% by local assessment of bone marrow aspirate and/or biopsy. For details refer to Appendix 1. 6. Karnofsky (age ≥16 years) or Lansky (age <16 years) performance status ≥60. 7. Adequate bone marrow reserve without transfusions (transfusion >2 weeks prior to laboratory assessment is allowed) defined as: a. Absolute neutrophil count (ANC) >1000/mm^3

<table>
<tr><td></td><td>
b. Platelets ≥50000//mm^3
c. Hemoglobin ≥8.0 g/dl
8. Adequate organ function:
a. a serum creatinine (sCR) based on gender/age as follows:
<table>
<tr><th colspan="3">Maximum Serum Creatinine (mg/dL)</th></tr>
<tr><th>Age</th><th>Male</th><th>Female</th></tr>
<tr><td>1 to <2 years</td><td>0.6</td><td>0.6</td></tr>
<tr><td>2 to <6 years</td><td>0.8</td><td>0.8</td></tr>
<tr><td>6 to <10 years</td><td>1.0</td><td>1.0</td></tr>
<tr><td>10 to <13 years</td><td>1.2</td><td>1.2</td></tr>
<tr><td>13 to <16 years</td><td>1.5</td><td>1.4</td></tr>
<tr><td>≥16 years</td><td>1.7</td><td>1.4</td></tr>
</table>
b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 times the upper limit of normal (ULN) for age
c. Total bilirubin <2 mg/dL (for Gilbert's Syndrome patients total bilirubin <4 mg/dL)
d. Adequate pulmonary function
i. Oxygen saturation of >91% on room air
ii. No or mild dyspnea (≤Grade 1)
9. Must have a leukapheresis material of non-mobilized cells accepted for manufacturing. Note: Leukapheresis material will not be shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria is received.
</td></tr>
<tr><td>Exclusion criteria</td><td>
Patients meeting any of the following criteria are not eligible for inclusion in this study.
1. Prior gene therapy or engineered T cell therapy
2. Prior treatment with any anti-CD19 therapy
3. Allogeneic hematopoietic stem cell transplant (HSCT) <3 months prior to screening and ≤4 months prior to infusion
4. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD) in patients who received prior allogeneic HSCT Appendix 6.
5. Prior diagnosis of malignancy other than study indication, and not disease free for 5 years
6. Clinically significant active infection confirmed by clinical evidence, imaging, or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, etc.)
7. Presence of active hepatitis B or C as indicated by serology. Repeat serology is required if the interval between serology performed at screening and tisagenlecleucel infusion exceeds 8 weeks. For detailed criteria see Appendix 2.
8. Human Immunodeficiency Virus (HIV) positive test. Repeat serology is required if the interval between serology performed at screening and tisagenlecleucel infusion exceeds 8 weeks
9. Active neurological autoimmune or inflammatory disorders not related to B cell NHL (eg: Guillain-Barre syndrome, Amyotrophic Lateral Sclerosis)
10. Active central nervous system (CNS) involvement by malignancy. Note: Patients with history of CNS disease that have been effectively treated will be eligible
</td></tr>
</table>

	11. Patients with B-cell NHL in the context of post-transplant lymphoproliferative disorders (PTLD) associated lymphomas 12. Patients with concomitant genetic syndromes associated with bone marrow failure status such as patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome. **Note:** Patients with Down syndrome will not be excluded. 13. Known hypersensitivity to the excipients of tisagenlecleucel or to any other drug product as advised for administration in the study protocol (e.g. lymphodepleting agents, tocilizumab) 14. Cardiac disorder defined as: a. Cardiac or cardiac repolarization abnormality, including any of the following: i. History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment ii. Clinically significant cardiac arrhythmias (eg: ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (eg: bifascicular block, Mobitz type II and third degree AV block) b. Left ventricular ejection fraction (LVEF) <45% as determined by echocardiography (ECHO) or magnetic resonance angiogram (MRA) or multigated acquisition (MUGA) c. New York Heart Association (NYHA) functional class III or IV (Chavey et al 2001) 15. Subjects enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies 16. Pregnant or nursing (lactating) women. **Note:** Women of child-bearing potential (WOCBP) must have a negative pregnancy test performed at screening, within 24 hours prior to leukapheresis, lymphodepletion, tisagenlecleucel infusion and at EOS 17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception from enrollment into this study through at least 12 months after the tisagenlecleucel infusion and until chimeric antigen receptor (CAR) T-cells are no longer present by qPCR on two consecutive tests. qPCR test results will be available upon request. 18. Sexually active males who do not agree to use a condom during intercourse from enrollment into this study through at least 12 months after the tisagenlecleucel infusion and until CAR-T-cells are no longer present by qPCR on two consecutive tests. qPCR test results will be available upon request.
Investigational treatment	The investigational treatment is an intravenous (iv) tisagenlecleucel infusion with a proposed dose range of 0.2 to 5 x 10^6 CAR-positive viable T cells per kg body weight (subjects ≤50 kg) or 0.1 to 2.5 x 10^8 CAR-positive viable T cells (subjects >50 kg).
Efficacy assessments	• Radiologic imaging • Bone marrow biopsy or aspirate • Cerebral spinal fluid (CSF) cytology • Physical exam findings/cytology/biopsy evaluation
Pharmacokinetic assessments	• Tisagenlecleucel cellular kinetics by qPCR and flow cytometry

Key safety assessments	• Physical examination • Vital signs • Adverse events (AE) • Clinical laboratory evaluations • Physical development • Performance status
Data analysis	• The primary efficacy analysis will be based on all evaluable subjects with aggressive r/r B-cell NHL who received an infusion of tisagenlecleucel. • [redacted] • The safety analysis will include all subjects with r/r B-cell NHL who received an infusion of tisagenlecleucel. The primary efficacy and safety analysis will be conducted when all evaluable subjects with aggressive r/r B-cell NHL have been infused and followed for at least 6 months from tisagenlecleucel infusion or discontinued early as well as at least 50% of those subjects have a follow-up of at least 9 months from tisagenlecleucel infusion or discontinued early.
Key words	Tisagenlecleucel, r/r B-cell NHL, pediatric patients, BL, DLBCL, PMBCL, GZL, FL, leukapheresis, lymphodepleting chemotherapy (LD)

[redacted]

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1.1 Overview of disease pathogenesis, epidemiology and classification

Lymphomas most commonly occur during the second decade of life, with a median age at diagnosis of 10 years 8 months, and is rare in infants (≤1 percent). The incidence increases with age as lymphomas account for approximately 4, 14, 22, and 25 percent of neoplasms in children 1 to 4, 5 to 9, 10 to 14, and 15 to 19 years of age, respectively (Kaatsch 2010). Non-Hodgkin lymphoma (NHL), a heterogeneous group of lymphoid malignancies, is the fourth most common malignancy diagnosed in children and accounts for approximately 7% of all childhood cancers in the developed world (Kaatsch 2010, Minard-Colin et al 2015). In the United States, approximately 750-800 new cases of childhood NHL are diagnosed annually with an estimated incidence of 10 to 20 cases per million people per year (Percy et al 1999). There is a male predominance, with the exception of primary mediastinal B-cell lymphoma, in which the incidence is similar among males and females. Childhood NHL is more common in whites than African Americans (Percy et al 1999, Attias et al 2009).

In adults, NHL typically presents as a low or intermediate grade disease, however, childhood NHL is usually an aggressive, poorly differentiated, disseminated disease, often invading extranodal sites, the bone marrow (BM), and central nervous system (CNS) in advanced stages. In order to determine the optimal management in childhood NHL, the grade and extent of disease must be established. The WHO classification for tumors of hematopoietic and lymphoid tissue (Campo et al 2011, Swerdlow et al 2016) represents the established guidelines for the diagnosis of malignant lymphomas and is based on the recognition of distinct diseases according to a combination of morphologic, immunophenotypic, genetic, molecular, and clinical features. About 90% of childhood NHL can be categorized as mature B-cell neoplasms, precursor lymphoid neoplasms of B- or T-cell lineage, and mature T-cell and NK-cell neoplasms. Among these categories, NHL is the most common, accounting for up to 60% of all newly diagnosed lymphomas in childhood and adolescence (Sandlund et al 1996, Burkhardt et al 2005).

Aggressive mature B-cell NHL consists mainly of Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and primary mediastinal large B-cell lymphoma (PMBCL). Pediatric follicular lymphoma (FL) is an indolent lymphoma which acts as a paradigm for the management of all indolent subtypes of NHL. Gray zone lymphomas are defined as lymphoid malignancies that cannot be reliably classified into a single disease entity after all available morphologic, immunophenotypic, and molecular investigations have been performed. The 2008 WHO classification proposed 2 gray zone lesions: (1) B-cell lymphoma, unclassifiable (BCLU), with features intermediate between DLBCL and BL and (2) B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma. In the 2016 revision to the WHO classification system, the category of BCLU with features intermediate between DLBCL and BL was eliminated, and all large B-cell lymphomas with *c-myc* and *BCL2*

[redacted]

and/or *BCL6* gene rearrangements have been identified as a distinct entity: high-grade B-cell lymphoma (HGBL) with rearrangement of *c-myc* and *BCL2* and/or *BCL6*. While there are numerous subtypes within the various categories of mature B-cell NHL, the treatment paradigm consists of more intensive regimens utilized for more aggressive disease as determined by stage and grade (Minard-Colin et al 2015).

Among the aggressive B-cell lymphomas, Burkitt lymphoma (BL) is the predominant malignancy, with the sporadic variant accounting for 40% of all childhood NHL in Western Europe and the United States (Mosse and Weck 2010). Tumor cells typically exhibit a mature B-cell phenotype and are negative for the enzyme terminal deoxynucleotidyl transferase (Tdt) and CD5, but do express surface immunoglobulin, (with either kappa or lambda light chains) and B-cell markers such as CD19, CD20, and CD10 (Minard-Colin et al 2015).

Burkitt lymphoma is characterized by translocation of the *c-myc* oncogene on chromosome 8q24 to one of the immunoglobulin gene loci regulatory elements (ie, IGH, IGK or IGL), resulting in the inappropriate overexpression of *c-myc* and malignant cell proliferation. The most common translocation associated with BL is t(8;14), resulting in translocation of *c-myc* to the IGm (mu) heavy chain gene (*IGH*) locus on chromosome 14q32, seen is approximately 80% of all BL cases. Less commonly, translocations between *c-myc* and the gene for either the kappa or lambda light chain, t(2;8) and t(8;22), respectively, can occur (Miles et al 2016). The 2016 WHO classification includes a distinct entity for the small subset of BL cases without MYC translocations, designated "Burkitt-like lymphoma with 11q aberration". While the clinical course appears to be similar to BL, lymphomas belonging to this subtype differ from BL in that they have a more complex karyotype, cytological pleomorphism and lower levels of MYC expression (Campo et al 2011).

Sporadic BL typically arises in the abdomen, lymphatic tissue of Waldeyer ring and head-neck region, although jaw involvement rarely occurs. Other sites of involvement include testes, bone, skin, pleural and peritoneal spaces. In advanced stages, BL presents with circulating lymphoma cells, bone marrow and CNS involvement, conferring a poorer prognosis. There has been considerable variability among staging systems in the classification of advanced disease in BL. Historically thought to represent different disease entities, the French-American-British (FAB) classification system categorized BL as small non-cleaved cell lymphoma or L3 acute lymphoblastic leukemia (ALL), depending on the presence of solid tumor/nodal mass or >25% bone marrow involvement, respectively. The WHO classification system recognized both phases as single disease entity, mature B cell neoplasm with subtype of Burkitt lymphoma or Burkitt cell leukemia, depending on the site of disease burden (Mosse and Weck 2010, Campo et al 2011). The recently revised International Pediatric Non-Hodgkin Lymphoma Staging System (Rosolen et al 2015) based on the initial St. Jude classification (Murphy 1980) describes stage IV BL as lymphoma with ≥5% to ≤25% bone marrow involvement and/or CNS involvement; >25% bone marrow involvement is defined as L3 ALL. Regardless of the classification system, treatment strategies are based on risk stratification and patients with bone marrow involvement are treated with regimens designed for BL (Woessmann et al 2005).

DLBCL in children and adolescents is a mature B-cell neoplasm, accounting for 10%-20% of childhood NHL; occurring with more frequency and aggressiveness during adolescence than during the first decade of life (Allen et al 2015). Immunophenotyping profile shows two different molecular patterns of DLBCL; activated B-cell-like (ABC) and germinal-center

B-cell-like (GCB). Whereas the adult DLBCL is frequently associated with the non-GCB phenotype, approximately two thirds of pediatric DLBCLs express the GCB molecular pattern with CD10 and BCL-6 positivity, which in part, may contribute to the better overall survival rates in children compared to adults (Oschlies et al 2006, Worch et al 2013). Furthermore, the t(14;18) rearrangements of the *IGH* and the *BCL2* genes commonly seen in adults is rarely seen in children and adolescent cases of DLBCL (Oschlies et al 2006). Instead, about 15% of a subset of pediatric DLBCL cases compared to 2% of adult cases, had a translocation that juxtaposed the *IRF4* oncogene next to one of the immunoglobulin loci, and this abnormality seemed to confer a better outcome (Salaverria et al 2011). Many of the DLBCL patients, particularly those younger than 14 years have a genetic profile similar to BL, characterized by a high frequency of abnormalities at the MYC locus (chromosome 8q24), including MYC rearrangement and overexpression; however, DLBCLs rarely have a proliferation index >95% (Miles et al 2008, Klapper et al 2008, Deffenbacher et al 2012). Of note, ID3-TCF3 pathway alterations associated with BL/B-cell leukemia (B-AL), were not observed in DLBCL (Miles et al 2016).

In DLBCL patients, CNS and/or bone marrow involvement is uncommon but when present CNS disease usually manifests as intracranial masses and is associated with poor prognosis (Salzburg et al 2007, El-Mallawany and Cairo 2015). Lymphomatous primary CNS disease without systemic involvement is uncommon in immunocompetent pediatric cases but more commonly seen with inherited or acquired immunodeficiency (Abla et al 2011).

Primary mediastinal (thymic) B-cell lymphoma (PMBCL), which is a separate entity from DLBCL, has histological and genetic features resembling the adult form, and accounts for approximately 2% childhood NHL cases (Oschlies et al 2011, Dunleavy and Wilson 2015). PMBCL is associated with chromosomal aberrations in chromosomes 9p and 2p, involving *JAK2* and *c-rel*, respectively, and is often associated with inactivation of *SOCS1* (Oschlies et al 2011, Bea et al 2005). These mediastinal tumors can be locally invasive and while dissemination outside the thoracic cavity can occur, CNS and bone marrow involvement are rare (Jaffe et al 2008).

According to the 2008 WHO classification of lymphomas (Campo et al 2011), pediatric FL is an indolent low-grade mature B-cell lymphoma affecting 1-2% of all pediatric lymphomas (Quintanilla-Martinez et al 2016, Liu et al 2013). Follicular lymphoma in children although morphologically similar to adult FL, displays significant differences from adult form in incidence, pathology and in expression of genetic markers. While adult FL is characterized by *IGH-BCL2*; t(14;18) (q32;q21) gene rearrangement and Bcl-2 overexpression, this is uncommon in children and when present is associated with an aggressive disease, unresponsive to treatment. FL in children has male predominance and is usually localized in the lymph nodes in the neck or tonsils, or may also present with extranodal involvement, and has an excellent prognosis with rare disease relapse and longer median survival rates with current therapies (Sandlund and Perkins 2015).

1.1.1.2 Current therapies and unmet medical need

Treatment in pediatric B-cell NHL consists of stage- and histology-directed multi-agent chemotherapy, with more intensive regimens utilized for more aggressive disease (Minard-Colin et al 2015). Although there are clinical and biological differences between BL and DLBCL, there is significant clinico-pathologic overlap among the mature B-cell NHL seen

[redacted]

in children, adolescents, and young adults. As such, similar treatment regimens have been used to treat both BL and large B-cell histologies, with no difference in outcome based on tumor histology, with the exception of PMBCL which has exhibited inferior outcomes (Gerrard et al 2013).

Outcomes for pediatric BL and DLBCL have greatly improved with intensive, short duration, pulsed courses of multi-agent chemotherapy, adapted to the disease stage (Reiter et al 1999, Woessmann et al 2005, Cairo et al 2007, Gerrard et al 2008, Minard-Colin et al 2015, Sandlund 2015). Newly diagnosed pediatric B-cell NHL patients are cured in the vast majority of cases, with rates approaching 80-90%, with standard available therapies (Minard-Colin et al 2015). However, there remains a high unmet medical need for patients with relapsed or refractory mature B-cell NHL (r/r B-cell NHL), as salvage therapies including hematopoietic stem cell transplant (HSCT), rituximab-based therapies and intensive chemotherapy regimens, offer limited clinical benefit and no therapies are currently accepted as the standard of care. Outcomes for this patient population are generally poor, with 5 year survival rates approaching 10-30% (Cairo et al 2007, Barth et al 2013, Minard-Colin et al 2015, Minard et al 2016).

A study conducted by the Children's Oncology Group (COG) evaluated the combination of rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) in r/r B-cell NHL. Twelve of 20 patients (60%) achieved partial or complete responses, the majority of whom (8/12, 67%) were alive at Follow-up of 13 to 30 months. Five of these 8 patients also received HSCT (Griffin et al 2009). However, patients who did not achieve a response (40%) to this treatment had a dismal prognosis with median overall survival of 2.5 months, highlighting the significant unmet medical need in this patient population for improved therapeutic options.

Hematopoietic stem cell transplant (HSCT) offers some survival benefit for r/r B-cell NHL patients able to achieve remission. The 5-year EFS patients who received either allogeneic (n=90) or autologous HSCT (n=92) after achieving a complete remission post conventional chemotherapy was 50-52% for DLBCL and 27-31% for BL (Gross et al 2010). However, chemo-resistance is a major problem, making remission difficult to achieve and therefore making patients ineligible for transplant (Bradley and Cairo 2008).

In a retrospective 10-year multicenter study from the United Kingdom, of the 33 children with r/r mature B-cell NHL, 9 patients (27.3%) survived, with a median Follow-up of 4.3 years. Patients who responded to either two cycles of CYVE (high-dose cytarabine and etoposide) or ICE (ifosfamide, carboplatin, and etoposide), each in combination with four doses of rituximab, followed by auto-HSCT had better survival outcomes compared to patients who were primary refractory or had early relapses. The investigators considered the possibility that the children who survived were those who remained well enough to tolerate and respond to immuno-chemotherapy followed by transplantation (Anoop et al 2012).

In a retrospective review of 1,322 pediatric B-cell NHL patients prospectively enrolled in the LMB-89, LMB-96, and LMB-2001 trials between July 1989 and March 2007, 67 patients were identified as having relapsed disease, defined as any tumor progression after having achieved a CR. In all 3 studies, the salvage therapy at relapse was determined based on the patient's initial disease stage and treatment regimen: patients with completely resected stage I and abdominal stage II (Group A), and patients with more advanced disease excluding stage IV with CNS involvement and mature B-cell leukemia (B-AL) (Group B), received CYVE with or without

[redacted]

high dose methotrexate; patients with stage IV with CNS involvement and B-AL (Group C) received VENOMID (vindesine, novantrone, methylprednisolone, ifosfamide), ICN (ifosfamide, carboplatin and novantrone) or ICE (ifosfamide, carboplatin, etoposide, and triple intrathecal therapy). Rituximab was added to the salvage therapy regimen for some patients after 1996. The overall response rate (ORR) was 65% (2 of 3 in group A, 19 of 29 in group B and 3 of 5 in group C achieved a CR/PR). Five-year OS was only 29.9% with a median Follow-up of 6.4 years (OS in groups A, B and C were 66.7%, 34.2%, and 17.4%, respectively). In responding patients, high-dose chemotherapy with stem cell transplant (SCT) improved survival, with both allogeneic and autologous transplant being equally effective, (OS of 38% and 49% respectively). However, patients not responding to initial salvage chemotherapy did not benefit from a further transplant. Also, rituximab addition did not offer significant survival benefit. Variables associated with improved survival rates were; single site of disease at relapse, large cell histology, initial low-risk disease (ie, group A or group B constituting stage I, II or III patients with normal lactate dehydrogenase (LDH)), and sustained remission >6 months, in a multivariate analysis of results (Jourdain et al 2015).

The Japanese Pediatric Leukemia/Lymphoma Study Group conducted a phase II study using R-ICE (n=22) or other rituximab based regimens (n=3) as first line salvage treatment in patients with r/r B-cell NHL (Osumi et al 2016). The 5-year OS in all patients receiving salvage therapy (n-33) was 48.5% with a median Follow-up of 5.9 years. The ORR (CR/PR) was 73% in patients treated with R-ICE regimen and a majority of them proceeded to receive HSCT. However, viral infections associated with allogeneic HSCT resulted in 4 deaths. Investigators considered that compromised immune function with B-cell aplasia resulting from prior rituximab therapy may have caused these fatal toxicities.

Consensus on the usefulness of rituximab and HSCT in pediatric patients with relapsed mature B-cell NHL has not been reached as only a handful of studies with modest responses are reported so far.

Considering the limited treatment options and poor prognosis for patients with r/r B-cell NHL, novel approaches are warranted to address the unmet need in this patient population for therapies that can achieve improved responses and overall survival.

1.1.2 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 possibly eliminate the patient's malignant cells. In particular, chimeric antigen receptor (CAR)-based approach involves engineering T cells with sequences that encode antibody-based antigen recognition moieties linked to signaling domains. Unlike T-cell receptors (TCR), CARs allow the T cells to specifically target and destroy tumor cells in a Major Histocompatibility Complex (MHC) independent manner (Mellman et al 2011).

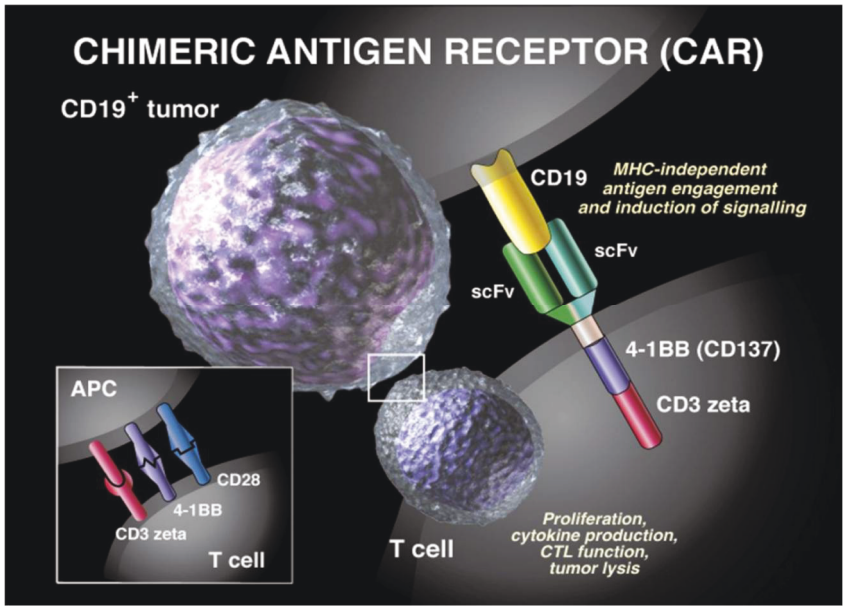
A promising target antigen for B-cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors (Sadelain et al 2003, Porter et al 2011), with no expression on hematopoietic stem cells or non-B cell tissues. It is a member of the immunoglobulin (Ig) superfamily 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 (CART-19), a second generation CAR, 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 lymphocytes transfected with a chimeric antigen receptor to combine the effector functions of T lymphocytes 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 and Pallavicini 2001).

Figure 1-1 Tisagenlecleucel chimeric antigen receptor design



Recent clinical trials of tisagenlecleucel in r/r chronic lymphoblastic leukemia (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 2019). 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 [Tisagenlecleucel Investigator's Brochure].
Abbreviation: antigen presenting cell (APC), CAR-T cell lymphocytes (CTL)

1.1.3 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, 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).

1.1.4 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 Investigational New Drug (IND) studies [Z2101I] and [B2002I]. In addition, there is 1 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 [Tisagenlecleucel Investigator's Brochure].

Clinical Cellular Kinetics

In adult r/r DLBCL subjects 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 subjects demonstrated expansion of transgene levels. Neither subject 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 (Mueller et al 2017).

The initial expansion of tisagenlecleucel and its prolonged persistence is required for initial as well as sustained disease response as was shown in pediatric and young adult ALL.

1.1.4.1 Clinical efficacy

Tisagenlecleucel is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of subjects up to 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse [Kymriah FDA 2017] and for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma [Kymriah FDA 2018].

Tisagenlecleucel is currently under evaluation by the European Medicines Agency (EMA) and other agencies for the treatment of adult subjects with refractory or relapsed DLBCL who are ineligible for autologous stem cell transplant, and for the treatment of pediatric and young adult subjects (up to 25 years) with refractory or relapsed B-cell ALL.

[redacted]

Efficacy in r/r pediatric and young adult ALL

Out of the 63 tisagenlecleucel-infused subjects, 52 (83%) achieved CR/Cri (complete remission with incomplete blood count recovery) within 3 months after **infusion**, and all of them were minimum residual disease (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

Two clinical trials with tisagenlecleucel in DLBCL subjects failing or not being candidates to HSCT are ongoing:

- CTL019A2101J (NCT02030834) (Schuster et al 2017a): this is a single-arm, single-institution trial ongoing at University of Pennsylvania. Patients with CD19+ DLBCL or FL with no curative treatment options, who relapsed, or had residual disease after autologous stem cell transplant (ASCT), or were not eligible for autologous or allogeneic HSCT, are eligible for trial. Patients had to have partial response or stable disease to most recent therapy. The 6-month ORR in DLBCL subjects was 50% (7/14 subjects), with CR achieved in 6 subjects (43%; 95% confidence interval (CI): 18-71%). Sustained remissions were achieved, and at a median Follow-up of 28.6 months, 86% of subjects with DLBCL who had a response (95% CI, 33 to 98) had maintained the response.
- CTL019C2201 (NCT02445428) (JULIET trial) (Schuster et al 2017b): this is a Novartis sponsored ongoing single-arm, multicenter trial. As of March 2017 cut-off, 99 subjects received a single dose of tisagenlecleucel. Median time from infusion to data cut-off was 3.7 months. Median age was 56 years (range 22-76). Fifty percent of the subjects received at least 3 prior lines of therapy, including 47% prior ASCT. Primary efficacy analysis based on 81 subjects showed clinically meaningful and durable responses including 53% overall response rate (ORR 37%, 30% CR). Median duration of response (DOR) and OS were not reached and most subjects achieving CR at Month 3 have remained in CR at data cut-off.

1.1.4.2 Clinical Safety

Section 4.5 outlines expected and potential toxicities related to tisagenlecleucel, most of which occur within 8 weeks of infusion.

Safety in r/r ALL

In subjects with r/r 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 subjects who received tisagenlecleucel, 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-cell NHL

In the recently approved CAR-T cell therapy for adult r/r DLBCL [Kymriah FDA 2018] based on study [CTL019C2201], among the 99 subjects 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 subjects required tocilizumab and 11% of subjects required corticosteroids

There were 16 subjects who died after tisagenlecleucel infusion. Three subjects died within 30 days of tisagenlecleucel infusion due to DLBCL; 13 subjects 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 profile observed in study C2201 was well characterized and manageable with close monitoring and established treatment algorithm (Schuster et al 2017b).

In study [CTL019A2101J], 36 subjects (20 DLBCL, 14 FL, and 2 mantle cell lymphoma (MCL)) were treated with tisagenlecleucel. There was one death (possibly related to tisagenlecleucel) in a subject with FL who died 234 days after tisagenlecleucel infusion in pathological CR (Schuster et al 2017a).

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) [BLA Clinical Review Memorandum Yescarta 2017].

For further information refer to the [Tisagenlecleucel Investigator's Brochure].

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 subjects with r/r ALL and in 4 adult subjects 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 qPCR detectable in any of the subject samples at time points up to 2 years following infusion (7 subjects from UPCC03712 trial; 16 subjects form UPCC04409 trial, 11 subjects from CHP959 trial).

1.2 Purpose

For the 10-20% of pediatric subjects who have r/r B-cell NHL, survival rates are dismal, only ~20-50% subjects are alive at 2 years with ORR of 20-30% after conventional salvage chemotherapy. Patients who respond to rituximab based chemotherapy (R-ICE), benefit from a subsequent transplant and achieve modest survival advantage (~30-50% EFS at 5 years).

However, those patients who are r/r to R-ICE (~40%) are not candidates for a transplant and have median overall survival of only 2.5 months. The purpose of the study is to assess the efficacy and safety of tisagenlecleucel in children, adolescents and young adults with r/r B-cell NHL.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoints(s) for primary objective(s)**
Evaluate the efficacy of tisagenlecleucel therapy as measured by ORR and determined by local investigator assessments in subjects with aggressive r/r B-cell NHL	Overall response rate (ORR), which includes complete response (CR) and partial response (PR) determined by local investigator assessments.
Secondary Objective(s)	**Endpoints(s) for secondary objective(s)**
Evaluate the duration of response (DOR) in subjects with aggressive r/r B-cell NHL	DOR is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented progression or death due to underlying cancer.
Evaluate event free survival (EFS) in subjects with aggressive r/r B-cell NHL	EFS is defined as the time from date of first tisagenlecleucel infusion to the earliest date of death from any cause, disease progression as determined by local investigator assessments, or starting new anticancer therapy for underlying cancer, excluding HSCT.
Evaluate relapse free survival (RFS) in subjects with aggressive r/r B-cell NHL	RFS is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented disease progression or death due to any cause.
Evaluate progression free survival (PFS) in subjects with aggressive r/r B-cell NHL	PFS is defined as the time from the date of first tisagenlecleucel infusion to the date of first documented disease progression as determined by local investigator assessments or death due to any cause
Evaluate overall survival (OS) in subjects with aggressive r/r B-cell NHL	OS is defined as the time from date of first tisagenlecleucel infusion to the date of death due to any cause.
Evaluate the safety of tisagenlecleucel therapy	Physical examination, vital signs, adverse events, laboratory abnormalities, performance status and as applicable physical development
Characterize the in vivo cellular kinetics (levels, expansion, persistence) of tisagenlecleucel cells into target tissues (blood, bone marrow, lymph nodes, cerebral spinal fluid and other tissues if available), as measured by qPCR in relation to safety and efficacy	Cellular kinetics parameters: Cmax, Tmax, AUCs, Clast, Tlast, and/or other relevant parameters in peripheral blood, bone marrow, lymph nodes, cerebrospinal fluid and other tissues as appropriate, Month 3 (±14 days) response, safety endpoint (CRS grade).

Objective(s)	Endpoint(s)
Characterize the presence of pre-existing and treatment induced immunogenicity and impact on cellular kinetics and response	Levels of pre-existing and treatment induced immunogenicity, cellular kinetic parameters, and efficacy (Month 3 (±14 days) response)
Assess the proportion of subjects who proceed to transplant post-tisagenlecleucel therapy until end of study (EOS)	Number of subjects that proceed to SCT after tisagenlecleucel infusion until EOS will be described
Retrospective assessment of potential CRS predictive models considering also data from other CTL019 trials	Assess the ability for early prediction of cytokine release syndrome utilizing clinical and biomarker data

[redacted]

3 Study design

This Phase II, single arm, multicenter, open label study to determine the safety and efficacy of tisagenlecleucel in pediatric subjects less than 18 years of age (and young adults aged equal or

[redacted]

less than 25 years) and weighing at least 6 kg with CD19+ r/r mature B-cell NHL, who have relapsed after one or more prior therapies (can include allogeneic and autologous HSCT) or have primary refractory disease (i.e. have not achieved a CR or PR after first line therapy), will have the following sequential phases for all subjects (Section 8):

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

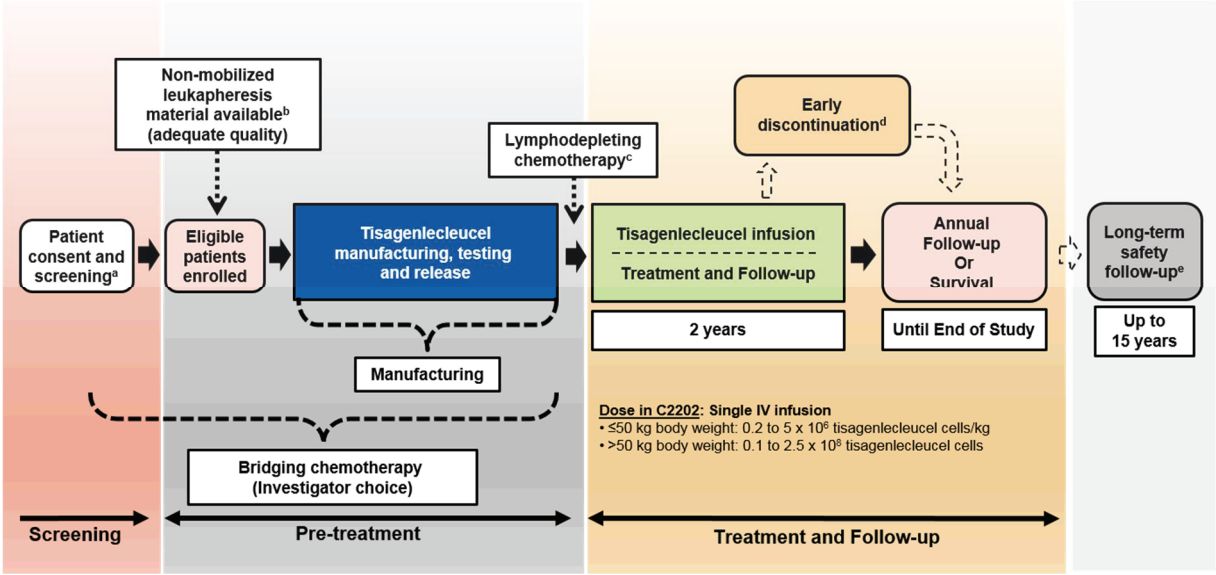
Screening begins after signing the study Informed Consent Form (ICF). Leukapheresis collection can begin after signing the consent. Non-mobilized leukapheresis material collected from the subject prior to study entry (historical) may be usable for tisagenlecleucel manufacturing if collected at an appropriately certified leukapheresis center and is of acceptable quality. Final enrollment is defined as the point at which a subject meets all inclusion/exclusion criteria and the subject's leukapheresis material is received and accepted for manufacturing. If the subject's leukapheresis collection is deemed unacceptable, the subject will screen fail. However, the subjects may be re-screened or re-apheresed as detailed under Section 8.1.

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

Treatment and Follow-up phase will include tisagenlecleucel infusion (Day 1) and the infused subjects will be followed according to the Assessment Schedule (Table 8-1) until **end of study (EOS)**. The investigational treatment contains 0.2 to 5 x 10^6 CAR-positive viable T-cells per kg body weight (subjects ≤50 kg) or 0.1 to 2.5 x 10^8 CAR-positive viable T-cells (subjects >50 kg) via an intravenous infusion. Subjects will be infused with the maximum cell dose within this range that can be individually manufactured. Efficacy assessments will be based on International Pediatric Non-Hodgkin Lymphoma Response Criteria (Sandlund et al 2015).

End of Study (EOS) is when all subjects complete the protocol defined 2-year treatment and follow-up phase and/or discontinue early. After end of study, all subjects will be asked to continue in a post-study long-term follow-up (LTFU) under a separate destination protocol [CCTL019A2205B], for up to 15 years post-infusion. Under this protocol, Follow-up for the lentiviral vector safety will continue as per the following health authority guidelines: FDA (2006a), FDA (2006b), European Medicines Agency (EMA) (2008) and EMA (2009).

Figure 3-1 Study Design



[a] Aggressive B-cell NHL subtypes (BL, DLBCL, PMBCL, GZL; N=26), in addition FL subjects may also be treated; age ≤25 years; r/r to one or more lines of prior therapies

[b] Previous leukapheresis collection or during screening

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

[d] Subjects that discontinue treatment and follow-up phase early (post-infusion but prior to M24 visit) will continue in Annual Follow-up or Survival Follow-up until End of Study (until all subjects who receive tisagenlecleucel complete 2 years of post-treatment phase or discontinue early).

[e] Conducted under a separate destination protocol

Efficacy will be evaluated by the investigator using computerized tomography/magnetic resonance imaging (CT/MRI) and positron emission tomography (PET)-CT or PET-MRI based on International Pediatric Non-Hodgkin Lymphoma (Sandlund et al 2015) response criteria clarified by Novartis for pediatric population (Appendix 1). Baseline disease assessment will be performed locally, at screening and repeated within two weeks prior to infusion. If local Health Authorities require the use of specific imaging modalities (eg: 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 Day 28 (as clinically indicated), Months 3, 6, 9, 12, 18, 24 post infusion and yearly thereafter or as clinically indicated until relapse or disease progression, death, lost to Follow-up, withdrawal of consent or EOS. Safety will be collected as per investigator assessment (as per Assessment Schedule in Table 8-1).

A post-study LTFU for tisagenlecleucel safety will continue under a separate destination protocol [CCTL019A2205B] per the following health authority guidelines: FDA (2006a), FDA (2006b), European Medicines Agency (EMA) (2008) and EMA (2009).

For the purpose of close safety monitoring of subjects in particular those with aggressive disease subtypes and for safely onboarding new sites, a staggered approach will be utilized at each site and will occur as follows:

- First subject infusion, wait 14 days

[redacted]

- Second subject infusion, wait 14 days
- Third subject infusion

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

Additional staggering will apply at the study level for subjects with a diagnosis of Burkitt leukemia at study entry and this will occur as follows:

- First Burkitt leukemia subject infusion on study, wait 14 days
- Second Burkitt leukemia subject infusion, wait 14 days
- Third Burkitt leukemia subject infusion

Following completion of this staggered infusion of the first three subjects with Burkitt leukemia, subsequent subjects will be treated in the study without staggering.

4 Rationale

4.1 Rationale for study design

This study is part of an agreed Pediatric Investigation Plan (PIP). The single-arm study design and sample size is justified by the rarity of r/r B-cell NHL subject population, poor prognosis, lack of approved effective therapies in this setting and limited recruitment to selected and specially trained tisagenlecleucel infusion centers.

Subject population will include aggressive subtypes of B-cell NHL. Therefore, subjects will be allowed to receive "bridging therapy" of investigator's choice to adequately manage their rapidly progressing underlying disease while they are screened for the study and/or after enrollment. Subjects with follicular lymphoma will be also included in the study. After assessment of eligibility, subjects qualifying for the study will be enrolled and are allowed to start lymphodepleting chemotherapy as recommended in protocol. Within 2-14 days of completion of lymphodepleting chemotherapy, tisagenlecleucel will be infused.

The efficacy of tisagenlecleucel will be evaluated through the primary endpoint of ORR which includes complete response (CR) and partial response (PR) as determined by local assessment. The choice of ORR as the primary endpoint is based on evidence that ORR is a standard outcome measurement in NHL (Cheson et al 2007).

Safety will be monitored in this trial closely in the first 1 month following tisagenlecleucel infusion and then every 3 months during the first year post-tisagenlecleucel infusion followed by semiannual assessment during the second year and annually thereafter until the EOS.

During the annual Follow-up phase of the study following Month 12 post tisagenlecleucel infusions only protocol defined AEs and adverse events of special interest (AESI) will be collected (Appendix 3). The frequency of safety monitoring and AESI are based on the clinical safety experience made in previous tisagenlecleucel studies.

[redacted]

4.1.1 Rationale for choice of bridging therapy

There are no standard treatment regimens recommended for the management of aggressive r/r B-cell NHL. Therefore, subjects will be allowed to receive bridging therapy per investigator's discretion. Medication restrictions prior to leukapheresis are provided in Section 6.2.2. It is recommended to complete bridging therapy 2 weeks before tisagenlecleucel infusion to allow for resolution of any toxicities.

4.2 Rationale for dose/regimen and duration of treatment

There is currently no clinical experience dosing pediatric B-cell NHL subjects with tisagenlecleucel. The recommended dose in this trial is based on experience from studies in pediatric ALL subjects. Clinical responses were observed across the wide range of CAR-positive cells infused including the lowest dose tested clinically. The dose-response, dose-safety, and dose-cellular kinetics analyses were performed using the data obtained from pediatric and young adult subjects with relapse/refractory ALL (B2202 and B2205J) 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 CTL019C2202.

- Dose-response and dose-exposure: Across the dose range studied, dose and exposure were independent.
- Dose-safety: The probability of any grade neurologic events and time to resolution of cytopenia were not impacted by dose. There was a 1.6 fold 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 CRS for dose of 5.0×10^8 cells and 6.0×10^8 cells were comparable, ie, 0.389 and 0.462, respectively. In addition, CRS is generally manageable in the study with the steps outlined in the CRS algorithm (Table 6-1).

Based on the totality of evidence from dose-safety, dose-efficacy, and exposure-response analyses, and the positive benefit risk ratio observed across the full range of doses, the dose specification mentioned as below will be utilized for Study CTL019C2202.

One of two possible CAR-positive viable T cell dose ranges will be prepared for the subject determined by the subject's weight during the leukapheresis visit or at baseline as follows:

- **Subjects ≤50 kg: 0.2 to 5.0 x 10^6 autologous CAR-positive viable T cells per kg body weight**
- **Subjects >50 kg: 0.1 to 2.5 x 10^8 autologous CAR-positive viable T cells**

Patients will be infused with the maximum cell dose within this range that can be individually manufactured.

Due to subject specific characteristics, batches outside of the manufacturing specification and/or the protocol recommended dose range may be produced. These batches will be evaluated to determine if they can be made available to the subject on a case by case basis, and these doses can be administered based on the benefit/risk assessment by the treating physician.

Please see [Tisagenlecleucel Investigator's Brochure] for further information on tisagenlecleucel dose selection in preclinical and clinical studies.

[redacted]

4.3 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T-cell proliferation (Dummer et al 2002), a recent 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 and Bevan 1999, Surh and Sprent 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 and Ahmed 2001, Van Stipdonk et al 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 interleukin (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 the addition of fludarabine to cyclophosphamide increased CAR-T cell expansion and persistence and improved disease free survival rates in adult subjects 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 subjects received lymphodepleting chemotherapy. Ninety-seven of these 99 subjects received fludarabine and cyclophosphamide.

4.4 Purpose and timing of interim analyses

Not applicable.

4.5 Risks and benefits

Appropriate eligibility criteria Section 5 are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs are provided in Section 6.6.2.

Tisagenlecleucel administered to over 500 subjects in clinical trials across the dose ranges tested has a well characterized safety profile in pediatric and young adult subjects. Even though there is currently no clinical experience treating pediatric B-cell NHL subjects with tisagenlecleucel, 3 pediatric and young adult r/r B-ALL studies and adult r/r DLBCL study have demonstrated a positive risk/benefit profile population. Therefore, it is expected that the potential benefit of tisagenlecleucel therapy in the pediatric B-cell NHL population in this study [CCTL019 C2202] may outweigh the potential risks. The long-term risks will also be monitored for up to 15 years post tisagenlecleucel in LTFU study [CCTL019A2205B] per health authority requirements.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs are provided in Section 6.6.2.

[redacted]

The risk to subjects in this trial may 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 [Tisagenlecleucel Investigator's Brochure]. In addition, stopping rules and monitoring by the Steering Committee (SC) are included in this protocol Section 10.2.5. There may be unforeseen risks with tisagenlecleucel which could be serious or potentially life threatening.

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

4.5.1 Identified safety risks

4.5.1.1 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 interferon gamma (IFN-γ), IL-6, tumor necrosis factor (TNF), ferritin, CRP, and IL-10. Severe and life-threatening events have been observed in subjects 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 4-1) and is graded according to the Lee Criteria (Table 4-2). Macrophage activation syndrome (MAS) is also associated with CRS as manifested by liver function test (LFT) abnormalities, cytopenias, and coagulopathy.

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

The onset of CRS should be retrospectively defined as the date of the first sign or symptom consistent with CRS. The resolution date of CRS should generally be declared resolved once fever, oxygen, and pressor requirements have resolved. Patients that receive anti-cytokine therapy or antipyretics may quickly resolve fever, however CRS should be considered ongoing even in the absence of fever until improvement of hemodynamic status and/or hypoxia with resolution of pressor and/or oxygen requirements. Concurrent or subsequent neurotoxicity is considered as a separate event (See section 4.5.1.2) and does not affect the grading or resolution of CRS. For example, necessity of intubation in those patients having a degree of neurotoxicity (e.g presence of seizure) where there is a concern for their ability to maintain a patent airway should not influence the grading or resolution of CRS (Lee et al 2019).

Table 4-1 Clinical signs and symptoms associated with CRS (modified from 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

Table 4-2 Cytokine Release Syndrome Grading (Lee et al 2014)

Grade	Toxicity
Grade 1	Symptoms are not life threatening and require symptomatic treatment only, e.g., fever, nausea, fatigue, headache, myalgia, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose* or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

*High dose vasopressor doses are shown in Table 6-2

A therapeutic strategy for the management of CRS is provided in Section 6.6.2.1 that should be followed.

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

[redacted]

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.

Early neurological events are the second most-common adverse reaction associated with CAR-T therapies. In attempt to standardize the assessment of these events, the CARTOX working group has suggested the name CART-cell- related- encephalopathy syndrome (CRES) (Neelapu et al 2018). This syndrome is described as a toxic encephalopathy with a wide range of variable symptoms such as aphasia, confusion, delirium, tremors, occasionally seizures and rarely life-threatening cerebral edema. The manifestation of CRES is biphasic, with the first phase occurring concurrently with CRS symptoms typically within the first 5 days after CAR-T-cell therapy, and the second phase after CRS subsides. Delayed neurological events with seizures or episodes of confusion 3-4 weeks following CAR-T-cell therapy have been reported to occur in approximately 10% of patients.

Although encephalopathy is a dominant feature of neurotoxicity following treatment with CAR-T cell therapy, there are other neurologic symptoms that should be taken into account. The American Society for Transplantation and Cellular Therapy (ASTCT) recently defined the term Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) as "a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema" (Lee et al 2019). A grading system was developed in order to characterize this syndrome (Table 4-4). For patients ≤12 years, the ICANS grading requires assessment of interactions via the Cornell Assessment of Pediatric Delirium (CAPD) (Table 4-5), whereas for patients > 12 years, it incorporates key aspects of the mini-mental status exam via the Immune effector Cell-associated Encephalopathy (ICE) score (Table 4-6).

In clinical trials, the majority of neurological events following tisagenlecleucel infusion were observed within 8 weeks, however, neurological events with later onset > 8 weeks and not in the context of CRS have also been reported. Most neurological events observed within 8 weeks were transient or self-limiting in nature. Frequently, encephalopathy, confusional state and delirium were observed. Other manifestations include a multifarious set of signs and symptoms including seizures, aphasia, speech disorder, and tremor. Some of the events are severe and may have a life-threatening outcome.

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 and prior history of CNS leukemia and history of other prior CNS diseases. 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.

[redacted]

The causality assessment of neurological events in subjects 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.

Table 4-3 Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grading (Lee et al, 2019)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score for age >12yr[^]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
CAPD score for age ≤12yr	<9	<9	≥9	Unable to perform CAPD
Depressed level of consciousness (any age)[v]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor weakness (any age)[§]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[#]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. For example, a patient with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.

[^] A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia. But a patient with an ICE score of 0 may be classified as having Grade 4 ICANS if the patient is unarousable.

[v] Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)

[§] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0 but they do not influence ICANS grading.

[redacted]

[#] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

CAPD: Cornell Assessment of Pediatric Delirium

Table 4-4 Encephalopathy Assessment for Children Age ≤12 Years Using the Cornell Assessment of Pediatric Delirium (CAPD) (Lee et al, 2019)

Answer the following based on interactions with the child over the course of the shift	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0
1. Does the child make eye contact with the caregiver?					
2. Are the child's actions purposeful?					
3. Is the child aware of his/her surroundings?					
4. Does the child communicate needs and wants?					
	Never 0	**Rarely 1**	**Sometimes 2**	**Often 3**	**Always 4**
5. Is the child restless?					
6. Is the child inconsolable?					
7. Is the child underactive – very little movement while awake?					
8. Does it take the child a long time to respond to interactions?					

Table 4-5 Immune effector Cell-associated Encephalopathy (ICE) score for Subjects Age >12 years (Lee et al, 2019)

Category	Test	Scoring
Orientation	Orientation to year, month, city, hospital	4 points total (1 point each)
Naming	Ability to name 3 objects (e.g. point to clock, pen, button)	3 points total (1 point each)
Following Commands	Ability to follow simple commands (e.g. "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing	Ability to write a standard sentence (e.g. "Our national bird is the bald eagle")	1 point

Category	Test	Scoring
Attention	Ability to count backwards from 100 by 10	1 point

For the management of neurological events see Section 6.6.2.2.

4.5.1.3 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 <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 al 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.

Subjects will have typically received lymphodepleting chemotherapy that is completed a few 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 6.6.2.3.

4.5.1.4 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 grade 3 in Common Terminology Criteria for Adverse Events (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 6.6.2.4.

4.5.1.5 Infections

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

- B-cell depletion is known to be associated with hypogammaglobulinemia that also contributes to the risk.
- Underlying bone marrow disease or dysfunction further increases the risk of infections
- Subjects with prolonged and profound immunosuppression may be at enhanced risk for more frequent and severe opportunistic infections. This may result from preceding anti-cancer treatment, such as radiation or chemotherapy, and lymphodepleting chemotherapy prior to treatment with tisagenlecleucel causing severe neutropenia and/or B-cell depletion from tisagenlecleucel.

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

4.5.1.5.1 Viral reactivation

Patients with active hepatitis B or active hepatitis C have been excluded from clinical studies with tisagenlecleucel, because of the potential risk of viral reactivation and the risk of fulminant hepatitis, hepatic failure and fatal outcome. Patients who are HIV positive have also been excluded, because of the possible effect on HIV viral suppression.

In addition, there is currently no experience with manufacturing tisagenlecleucel for patients testing positive for HBV, HCV and HIV. Patients are to be screened for any active HBV, HCV or HIV infection prior to leukapheresis.

Subjects with active hepatitis B or hepatitis C or with 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 6.6.2.5.

4.5.1.6 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 white blood cell (WBC) count >1000 cells/µL, febrile neutropenia is seen in subjects 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 6.6.2.6.

4.5.1.7 Prolonged depletion of normal B cells and hypo- or 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 subjects. 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.

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

A therapeutic strategy for the management of B cell depletion with resulting hypo-gammaglobulinemia is provided in Section 6.6.2.7.

4.5.1.8 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.

Subjects 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.

A therapeutic strategy for the management of hematopoietic cytopenias is provided in Section 6.6.2.8.

[redacted]

4.5.2 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.

4.5.2.1 Cerebral edema (fatal)

No fatal cerebral edemas have been reported within three weeks following tisagenlecleucel infusion in the clinical development program or the post-marketing setting to date that would resemble five fatal events reported for JCAR015 in the ROCKET study. JCAR015 presents a very different construct of an anti-CD19 CAR-T cell product compared to tisagenlecleucel. These five fatal cases of cerebral edema were characterized by a rapid evolution soon after JCAR015 infusion, appeared to be resistant to anti-cytokine treatment, and ensued brain death within 1-2 days after diagnosis. Following a retrospective exploratory analysis of these five cases, it is believed that these fatal cerebral edemas emerged from rapid T-cell expansion associated with the specific CAR-T cell product construct that determines the kinetics of T-cell expansion after infusion together with other risk factors such as high baseline blood levels of IL-15 (Gilbert 2017). Key findings of this retrospective analysis of the JCAR015 cases with fatal cerebral edema showed that all five patients experienced rapid, early expansion of their CAR-T cells within a week of being infused (rather than the typical time frame of 12-14 days), high levels of the CD8+ subtype and, consequently, a sharp spike in cytokines such as IL-2 and TNFα. Autopsy results from two of the patients showed a breakdown of the blood-brain barrier, possibly due to inflammatory cytokine surge. Potential baseline risk factors included age younger than 30 years, Philadelphia chromosome negativity, subset of disease (ie, B-ALL), fewer prior regimens, higher levels of IL15 and decreased levels of platelets (Gust et al 2017).

Since the five fatal cases after exposure to the JCAR015 product have become known, another patient with fatal cerebral edema was reported in the ZUMA-1 trial following KTE-019 infusion that may be worthwhile to mention for completeness. This patient progressed to CRS grade 4 refractory to tocilizumab and dexamethasone on Day 4, developed cerebral edema that was refractory to siltuximab and mannitol on Day 9, and died on Day 11 (Turtle et al 2017). The clinical course of this case treated with KTE-019 may not be comparable with those 5 cases treated with JCAR015, which is further supported by a retrospective analysis of baseline cytokine and chemokine levels in serum and cerebrospinal fluid suggesting significant pre-existing underlying inflammatory condition providing an alternate explanation [BLA Clinical Review Memorandum Yescarta 2017].

4.5.2.2 Replication competent lentivirus (RCL) production

Replication-competent lentivirus (RCL) could theoretically 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 subject.

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 subjects 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 subjects and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial (see [Novartis Product Handling Manual for Clinical Trials: CAR-T Products] for a description of the assays). Since the probability and characteristics of an RCL are unknown, no regulatory guideline for the management of RCL positive subjects exist to date.

As per guidance for gene therapy medicinal products, subjects exposed to tisagenlecleucel will be monitored for 15 years following last treatment for vectors persistence and RCL within the LTFU study.

The Management of this potential risk is addressed in Section 6.6.2.9.

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

Secondary malignancies in cancer patients, i.e., newly occurring malignancies other than the primary malignancy (e.g., T-cell and non-T-cell hematological malignancies, solid tumors), can be increased as a result of both previous chemotherapy and radiation therapy exposure and partly due to increased rates within families (Freidman et al 2010). The rate of new malignancy detection following tisagenlecleucel therapy will need to take into account these additional confounding risk factors.

Transduction of a patient's T cells with the lentiviral vector could lead to insertional mutagenesis resulting in an uncontrolled T-cell proliferation and an oncogenic effect that could result in a T-cell and may be non-T-cell malignancies.

Ruella et al (2018) reported a B-cell ALL patient treated in an early clinical study at the University of Pennsylvania (Penn) / Children's Hospital of Philadelphia with CTL019 as manufactured by Penn. The patient showed an initial response to treatment and relapsed 9 months after infusion with CD19-negative leukemia cell that aberrantly expressed the anti-CD19 CAR. The CAR gene was unintentionally introduced into a single leukemic B cell during CAR-T cell manufacture at Penn and its product bound in cis to the CD19 epitope on the surface of leukemic cells, masking it from recognition by and conferring resistance to the CAR-T.

The Novartis manufacturing process for tisagenlecleucel is designed to significantly reduce the probability of contaminating B cells in the T cell culture. Therefore, the risk of CAR transduction of B cells as observed at the early CTL019 study at Penn and described in the publication by Ruella et al (2018) can be considered low with the current Novartis manufacturing process.

Tisagenlecleucel uses third generation self-inactivating lentiviral vector. Insertional mutagenesis was addressed in two lentivirus insertion site analysis (LISA) studies where 12 batches of tisagenlecleucel ready for infusion and two batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration

[redacted]

near genes of concern, no preferential sites of integration (hottest lesion), 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 et al 2002, Dudley et al 2005).

The management of this potential risk is addressed in Section 6.6.2.10.

4.5.2.4 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). Prior chemotherapy and radiation also contribute to the risk.

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

4.5.2.5 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.

[redacted]

4.5.2.6 Graft versus host disease (GVHD)

The chance of graft versus host disease (GVHD) occurring in subjects is low, but it is a potential risk with tisagenlecleucel therapy in subjects 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 subjects with grade 3 GVHD and none with grade 4) (Porter et al 2006). Of 18 ALL subjects 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 6.6.2.11.

4.5.2.7 Transmission of infectious agents

Transmission of infectious agents could lead to new infections and reactivation of pre-existing viral disease (e.g., HBV, HCV, or HIV), respectively, in close contacts including personnel involved in the tisagenlecleucel manufacturing process, health care providers involved in leukapheresis and administering tisagenlecleucel or the patients treated with tisagenlecleucel.

Multiple steps are required to produce tisagenlecleucel CAR-T-cells, involving leukapheresis to obtain patient autologous starting material, enrichment and activation, gene transduction via lentiviral vector and expansion. Transmission of infectious material via product could potentially derive from the patient's own leukapheresis material prepared from autologous blood, other material including the tisagenlecleucel viral vector required to manufacture tisagenlecleucel, through contamination during the manufacturing process or inadequate storage. Due to the nature of the product (i.e., cells), there is no possibility to introduce terminal sterilization or dedicated viral removal and inactivation steps. Stringent precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of tisagenlecleucel are in place in compliance with principles of good manufacturing practices and regulatory guidelines.

The risk associated with tisagenlecleucel is considered low.

4.5.2.8 Decrease in cell viability due to inappropriate handling of the product

Inappropriate handling of the manufactured product including transport, storage in addition to thawing and standing time prior to infusion may result in a decrease of viable cells. This may impact the efficacy and safety of tisagenlecleucel. Qualified center personnel must follow appropriate protocols for product handling to receive, thaw, and infuse the finished tisagenlecleucel product. Please refer to the [Novartis Leukapheresis, Cryopreservation, and Scheduling Manual for Clinical Trials: CAR-T Product].

4.5.3 Other risks

4.5.3.1 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

[redacted]

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.

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 subject 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.

5 Population

The target patient population participating in the study will include male and female, pediatric patients (<18 years of age, weighing at least 6 kg) as well as adolescent and young adult patients (≤25 years of age) with CD19+ r/r mature B-cell NHL, including broad histological aggressive subtypes based on the WHO classification (Swerdlow et al 2016), such as BL, DLBCL, PMBCL, GZL and FL who have relapsed after one or more prior therapies or are primary refractory (have not achieved a CR or PR after the first line of therapy). Patients who have progressed after prior allogeneic and autologous HSCT are allowed to participate in the study.

It is planned to enroll approximately 35 patients with an aim to have 26 infused and evaluable patients (of these at least 18 subjects less than 18 years of age) with aggressive subtypes of r/r B-cell NHL available for the primary analysis. There is no pre-specified target for the number of pediatric FL patients to be treated because it is an extremely rare disease type. However enrollment in this subtype will be open until 26 patients with the aggressive subtypes have been infused and are evaluable for primary analysis. It is anticipated that the life expectancy of enrolled patients is at least 12 weeks or more.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria at screening and prior to infusion are offered treatment in the study.

5.1 Inclusion criteria

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

1. Signed informed consent and assent forms if applicable must be obtained prior to participation in the study.
2. Histologically confirmed (local evaluation) mature B-cell non-Hodgkin lymphoma (B-cell NHL) including the following subtypes; Burkitt Lymphoma and Burkitt Leukemia (L3 B-ALL) (BL), Diffuse Large B-Cell Lymphoma (DLBCL), Primary Mediastinal B-Cell Lymphoma (PMBCL), Gray Zone lymphoma (GZL), and Follicular Lymphoma (FL).
   Note: Patients with B-cell NHL associated with Nijmegen breakage syndrome will be allowed.
   a. Sufficient formalin-fixed, paraffin-embedded (FFPE) tumor sample must be available for correlative analyses. A recent tumor sample obtained for the purpose of the study must be submitted, however if not clinically feasible, an archival tumor biopsy from the most recent relapse or other historical sample may be submitted instead. Excisional biopsies should be submitted wherever possible; in cases where this is not possible a core needle biopsy is allowed. Fine needle aspiration (FNA) is not suitable.
3. Patients ≤25 years of age and weighing at least 6 kg at the time of screening.
4. Patients who have relapsed after one or more prior therapies (can include allogeneic and autologous hematopoietic stem cell transplant) or are primary refractory (have not achieved a CR or PR after the first line of therapy).
5. Measurable disease by radiological criteria in all patients at the time of screening. Patients with Burkitt leukemia who don't meet radiological criteria must have bone marrow involvement of >25%. For details refer to Appendix 1.
6. Karnofsky (age ≥16 years) or Lansky (age <16 years) performance status ≥60.
7. Adequate bone marrow reserve without transfusions defined as:
   a. Absolute neutrophil count (ANC) >1000/mm^3
   b. Platelets ≥50000//mm^3
   c. Hemoglobin ≥8.0 g/dl

   Note: These criteria do not apply for subjects with Burkitt leukemia.
8. Adequate organ function:
   a. a serum creatinine (sCR) based on gender/age as follows:

Maximum Serum Creatinine (mg/dL)		
Age	**Male**	**Female**
1 to <2 years	0.6	0.6
2 to <6 years	0.8	0.8
6 to <10 years	1.0	1.0
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥16 years	1.7	1.4

   b. AST (aspartate aminotransferase) and ALT (alanine aminotransferase) ≤5 times the upper limit of normal (ULN) for age.
   c. Total bilirubin <2 mg/dL (for Gilbert's Syndrome patients total bilirubin <4 mg/dL).
   d. Adequate pulmonary function
      i. Oxygen saturation of >91% on room air.
      ii. No or mild dyspnea (≤Grade 1)
9. Must have a leukapheresis material of non-mobilized cells accepted for manufacturing. **Note:** Leukapheresis material will not be shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria is received.

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. Prior gene therapy or engineered T cell therapy
2. Prior treatment with any anti-CD19 therapy
3. Allogeneic hematopoietic stem cell transplant (HSCT) <3 months prior to screening and ≤4 months prior to infusion
4. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD) in patients who received prior allogeneic HSCT Appendix 6.
5. Prior diagnosis of malignancy other than study indication, and not disease free for 5 years
6. Clinically significant active infection confirmed by clinical evidence, imaging, or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, etc.)
7. Presence of active hepatitis B or C as indicated by serology. Repeat serology is required if the interval between serology performed at screening and tisagenlecleucel infusion exceeds 8 weeks. For detailed criteria see Appendix 2.
8. Human Immunodeficiency Virus (HIV) positive test. Repeat serology is required if the interval between serology performed at screening and tisagenlecleucel infusion exceeds 8 weeks
9. Active neurological autoimmune or inflammatory disorders (eg: Guillain-Barre syndrome, Amyotrophic Lateral Sclerosis)
10. Active CNS involvement by malignancy. **Note:** Patients with history of CNS disease that have been effectively treated will be eligible.
11. Patients with B-cell NHL in the context of post-transplant lymphoproliferative disorders (PTLD) associated lymphomas.

[redacted]

12. Patients with concomitant genetic syndromes associated with bone marrow failure status such as patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome. **Note:** Patients with Down syndrome will not be excluded.
13. Known hypersensitivity to the excipients of tisagenlecleucel or to any other drug product as advised for administration in the study protocol (e.g. lymphodepleting agents, tocilizumab)
14. Cardiac disorder defined as:
    a. Cardiac or cardiac repolarization abnormality, including any of the following:
        i. History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
        ii. Clinically significant cardiac arrhythmias (eg: ventricular tachycardia), complete left bundle branch block, high-grade AV block (eg: bifascicular block, Mobitz type II and third degree AV block)
    b. LVEF <45% as determined by ECHO or MRA or MUGA
    c. NYHA functional class III or IV (Chavey et al 2001)
15. Subjects enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies
16. Pregnant or nursing (lactating) women.

    Note: Women of child-bearing potential (WOCBP) must have a negative pregnancy test performed at screening, within 24 hours prior to leukapheresis, lymphodepletion, tisagenlecleucel infusion and at EOS.
17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception from enrollment into this study through at least 12 months after the tisagenlecleucel infusion and until CAR-T cells are no longer present by qPCR on two consecutive tests. qPCR test results will be available upon request. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg: 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 bilateral tubal ligation at least six weeks before enrollment. 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 subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - 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.

[redacted]

Additional considerations:

- 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 (eg: age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral [redacted] 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.
  Note: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

18. Sexually active males who do not agree to use a condom during intercourse from enrollment through at least 12 months after the tisagenlecleucel infusion and until CAR-T cells are no longer present by qPCR on two consecutive tests. qPCR test results will be available upon request.
    Note: 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.

6 Treatment

6.1 Study treatment

Study treatments will include lymphodepleting chemotherapy (if given) and tisagenlecleucel (investigational drug).

6.1.1 Investigational drugs

Tisagenlecleucel is an autologous cellular immunotherapy product that is comprised of CD3+ T cells that have undergone ex vivo T cell activation, genetic 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 subject 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. The transduced cells are expanded *ex vivo*. At the end of the culture, the 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.

For details please refer to the [Novartis Product Handling Manual for Clinical Trials: CAR-T Products] and the current version of the [Investigator Brochure].

[redacted]

6.1.2 Tisagenlecleucel dosing regimen

The investigational treatment is intravenous tisagenlecleucel with a proposed dose range of 0.2 to 5 x 10^6 CAR-positive viable T cells per kg body weight (subjects ≤50 kg) or 0.1 to 2.5 x 10^8 CAR-positive viable T cells (subjects >50 kg).

In rare cases tisagenlecleucel may present with out-of- specification results from the release testing. Where the administration of the product is necessary to avoid an immediate significant hazard to the subject and taking into account the alternative options for the subject and the consequences of not receiving tisagenlecleucel, the supply of the product may be justified upon request from the treating physician. Tisagenlecleucel will then be provided based on the evaluation of the risks and the confirmation of the treating physician to accept the product.

6.1.3 Pre-infusion evaluation

If the time since any assessment completed at screening for clinical eligibility has exceeded its required specified window (as detailed in Section 8.1), the assessment must be repeated prior to tisagenlecleucel infusion. If the period of delay is more than 4 weeks from completing lymphodepletion and there is no significant cytopenia (see Section 6.1.5.2), lymphodepletion should be repeated, and these criteria will need to be re-checked prior to tisagenlecleucel infusion.

If any of the following criteria is met, tisagenlecleucel infusion must be delayed until resolution:

1. Rapidly progressing or uncontrolled B-cell NHL
2. Active and/or uncontrolled TLS despite medical intervention
3. Active CNS involvement by malignancy
4. Laboratory abnormalities that, in the opinion of the investigator, may impact subject safety or the subjects' ability to receive tisagenlecleucel.
5. Following clinical abnormalities:
    - Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 91% or presence of progressive radiographic abnormalities on chest x-ray
    - Cardiac arrhythmia not controlled with medical management
    - Hypotension requiring pressor support
    - Active infection, as evidenced by positive blood cultures for bacteria, fungi, or polymerase chain reaction (PCR) positivity for viral DNA in blood within 72 hours of tisagenlecleucel cell infusion, or clinical or radiographic evidence
    - Active graft versus host disease (GVHD) Appendix 6.
6. Allogeneic hematopoietic stem cell transplant (HSCT) ≤4 months prior to tisagenlecleucel infusion
7. A significant change in clinical status that would, in the opinion of the investigator, increase the risk of adverse events associated with tisagenlecleucel
8. Significant toxicities from chemotherapy (including lymphodepletion) that would, in the opinion of the investigator, increase the risk of adverse events associated with tisagenlecleucel.
9. Prohibited medications and non-drug therapies as described in Section 6.2.2.

[redacted]

10. Positive influenza test within 10 days prior to tisagenlecleucel infusion (please refer to Table 8-1). If the subject 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 subject 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 subject is asymptomatic. For subjects residing in the United States, Canada, Europe and Japan, influenza testing is required during the months of October through May (inclusive). For subjects residing in the southern hemisphere such as Australia, influenza testing is required during the months of April through November (inclusive). For subjects with significant international travel, both calendar intervals above may need to be considered.
11. Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours prior to tisagenlecleucel infusion.

6.1.4 Additional safety procedures prior to tisagenlecleucel infusion

Tumor lysis syndrome (TLS)

The risk of TLS is dependent on disease burden. Subjects will be closely monitored both before and after lymphodepleting chemotherapy and the tisagenlecleucel infusion, including blood tests for potassium, creatinine, calcium, phosphorous, and uric acid. Subjects with elevated uric acid or high tumor burden will receive prophylactic allopurinol, or a non-allopurinol alternative (eg: febuxostat).

For further recommendations regarding the management of TLS, please refer to Section 6.6.2.4.

Infections

Infection prophylaxis should follow local guidelines dictated only by the preceding lymphodepleting chemotherapy.

Cytokine Release Syndrome

A minimum of two doses of tocilizumab per subject for use in the event of cytokine release syndrome and emergency equipment must be available on site prior to infusion. Treatment centers should have timely access to additional doses of tocilizumab (see Section 6.6.2.1 /Cytokine Release Syndrome (CRS) for details). See full Prescribing Information to use tocilizumab safely and effectively [local Actemra Prescribing Information].

Premedication

Side effects from T cell infusions can include fever, chills and/or nausea. All subjects should be pre-medicated with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine approximately 30 to 60 minutes prior to infusion. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed if the subject continues to have fever not relieved with acetaminophen (paracetamol). Steroids should NOT be used for premedication. It is recommended that subjects should 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.

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. Subjects should be evaluated and carefully monitored until complete resolution of signs and symptoms. Subject or subject's caregiver should monitor the subject's temperature twice a day for the first 3-4 weeks. Subjects are required to stay near the treatment site for the first 4 weeks. The subject or subject's caregiver should be instructed to call the investigator promptly with any signs of fever for possible hospitalization.

Supportive care: Local guidelines will be followed for the supportive care of immunosuppressed and chemotherapy treated subjects. All blood products administered should be irradiated. For details about prohibited concomitant medications and non-drug therapies please refer to Section 6.2.2.

6.1.5 Additional treatments

6.1.5.1 Bridging therapy

While awaiting completion of tisagenlecleucel product manufacturing, those subjects who may need additional (bridging) therapy to control their disease, based on the extent of the disease burden and per investigator's discretion, may receive appropriate treatment. Medication restrictions prior to leukapheresis are provided in Section 6.2.2. It is recommended that bridging therapy be completed 2 weeks prior to tisagenlecleucel infusion.

6.1.5.2 Lymphodepleting chemotherapy

Prior to tisagenlecleucel infusion, each subject should undergo lymphodepletion, unless the subject has a significant cytopenia (eg: WBC <1000 cells/µL, absolute lymphocyte count <200/µL) or any condition that, in the investigator's opinion, precludes lymphodepletion. Female subjects of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the start of lymphodepleting therapy (if >8 weeks from the last test). If the subject does not require lymphodepleting therapy, she should still have a negative serum pregnancy test at the required visit that takes place within 24 hours prior to tisagenlecleucel infusion.

Lymphodepletion should start such that tisagenlecleucel will be infused 2 to 14 days after completion of lymphodepletion depending on the lymphodepleting regimen. Lymphodepletion may be repeated in case tisagenlecleucel has been delayed by more than 4 weeks (see Section 6.1.3. The preferred regimen is as follows:

- Fludarabine (30 mg/m^2 intravenously (i.v.) daily for 4 days)
- Cyclophosphamide (500 mg/m^2 i.v. daily for 2 days starting with the first dose of fludarabine)

Side effects of fludarabine include severe neurological 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. Fludarabine may also severely decrease bone marrow function (fludarabine full prescribing information).

Cyclophosphamide can cause 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. High doses of cyclophosphamide led in a few instances to severe, and sometimes fatal, congestive heart failure after the first 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 a subject has a history of grade 4 hemorrhagic cystitis with cyclophosphamide or of resistance to a cyclophosphamide-containing regimen, then the following regimen should be used:

- Cytarabine (500 mg/m^2 i.v. daily for 2 days) and
- Etoposide (150 mg/m^2 i.v. daily x 3 days starting with the first dose of cytarabine)

Refer to the prescription information for toxicities associated with cytarabine and etoposide.

6.1.6 Treatment duration

A single dose of tisagenlecleucel will be given within 30 minutes after thawing of the product. For more details please refer to [Novartis Product Handling Manual for Clinical Trials: CAR-T Products].

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Collection of therapy within 30 days of screening

Clinically significant prescription and nonprescription medication, excluding vitamins, and herbal and nutritional supplements, procedure-related (inpatient or outpatient) medications and therapy taken by the subject during the 30 days prior to screening will be recorded.

Collection of concomitant therapy from screening to end of study

At every visit following the screening visit up to the end of the study, concomitant medications and therapy will be recorded in the medical record on the appropriate CRF. During selected trial phases, concomitant medication collection will be modified as outlined in Appendix 3: Tisagenlecleucel modified data reporting 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.

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Forms (CRF).

[redacted]

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before enrolling a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Modified data capture of concomitant treatments for inpatient/in hospital events

A significant number of tisagenlecleucel treated subjects will require multiple days of inpatient and/or intensive care unit (ICU) care within 28 days after tisagenlecleucel infusion. These AEs are mostly due to CRS and MAS, although there may be also contribution from the preceding lymphodepleting chemotherapy (eg: events such as febrile neutropenia or hematopoietic cytopenias). Cytokine release syndrome/MAS toxicity is an 'on-target' effect of the tisagenlecleucel cell expansion, activation and tumor cell killing.

A typical inpatient or ICU day can generate hundreds of data points and many therapeutic dose changes throughout a given day. These inpatient events and days are not scheduled protocol defined visits, although they are anticipated to occur in some subjects. Revised inpatient data capture will be utilized for this study to systematically collect subsets of subject data to describe the management of safety events associated with tisagenlecleucel therapy for the purpose of:

- Adequately informing physicians and subjects of the expected risks of tisagenlecleucel and the recommended interventions to manage these risks
- Health authority submission

This is done through a targeted collection of concomitant medications and laboratory data and CRS eCRF pages specifically designed to capture tisagenlecleucel related toxicity, severity, seriousness, causality, interventions and response/resolution following intervention. Details can be found in the CRF Completion Guidelines (CCGs).

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

The subject 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.

6.2.2 Prohibited medications and non-drug therapies

Medication restrictions prior to leukapheresis

The subject must be asked to notify the investigational site about any new medications he/she takes after the start of the study drug. 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.

Subjects may receive the following medications prior to leukapheresis in order to stabilize the disease:

1. Therapeutic doses of steroids may be given for up to 1 week but must be stopped >72 hours prior to leukapheresis.

[redacted]

2. Low-dose daily chemotherapy may be given for up to 1 week but must be stopped > 72 hours prior to leukapheresis.

For all other medication restrictions before leukapheresis, please refer to the recent [Novartis Leukapheresis, Cryopreservation, and Scheduling Manual for Clinical Trials: CAR-T Product].

Medication restrictions prior to and post 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: <12 mg/m^2/day hydrocortisone or equivalent.
2. **Steroids or other immunosuppressant drugs** are not recommended to be used as pre-medication for tisagenlecleucel therapy 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 (eg: rituximab) should not be used within 2 weeks prior to tisagenlecleucel infusion
4. **CNS disease prophylaxis or intrathecal therapy** must be stopped >1 week prior to tisagenlecleucel infusion (eg: intrathecal methotrexate)
5. **Radiation therapy** must be stopped >2 weeks prior to tisagenlecleucel infusion. Cranial radiation must be stopped >8 weeks prior to tisagenlecleucel infusion.
6. **Live vaccines** must not be used in tisagenlecleucel recipients for at least 6 weeks prior to lymphodepletion and during tisagenlecleucel treatment until immune recovery following treatment with tisagenlecleucel.
7. Granulocyte macrophage-colony stimulating factor (GM-CSF) has the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.
8. **Antiproliferative therapies**, other than lymphodepletion including low dose daily or weekly maintenance chemotherapy should not be used within 2 weeks prior to infusion.
    - Short acting drugs used to treat primary disease (eg: hydroxyurea, tyrosine kinase inhibitors) must be stopped >72 hours prior to tisagenlecleucel.
9. **GVHD therapies:** In subjects with allogeneic HSCT, any systemic drug used for GVHD prophylaxis must be stopped >2 weeks prior to tisagenlecleucel infusion to confirm that GVHD recurrence is not observed (eg: calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as rituximab, anti-TNF, anti-IL6 or anti-IL6R, systemic steroids)

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center

[redacted]

Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject. If the subject fails to start treatment for any reason, the reason will be entered into the appropriate CRF page. For detailed screening and enrollment procedures, related to the use of Interactive Response Technology (IRT), please refer to the [IRT User Manual].

6.4 Treatment Blinding

Not applicable.

6.5 Dose escalation and dose modification

Not applicable as subjects will receive a single intravenous (i.v.) infusion of CAR-positive viable T cells.

6.5.1 Follow-up for toxicities

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

Subjects with transaminase increase combined with total bilirubin (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 subject's baseline AST/ALT and TBIL value; subjects meeting any of the following criteria will require further Follow-up as outlined below:

- For subjects 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 subjects 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 alkaline phosphatase (ALP) elevation >2.0 x ULN with ALT/ALP x ULN (R value) <2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects 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 ≤2), hepatocellular (R ≥5), or mixed (R >2 and <5) liver injury).

In the absence of cholestasis, these subjects 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 and direct bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/International Normalized Ratio (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 (eg: biliary tract) may be warranted.
4. Obtain pharmacokinetic (PK) sample, as close as possible to last dose of tisagenlecleucel, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (cytomegalovirus (CMV), Epstein-bar virus (EBV) or Herpes simplex virus (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 significant”, thus, met the definition of serious adverse event (SAE) and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Novartis has established methods to ensure full traceability between the subject’s autologous leukapheresis and the tisagenlecleucel product in line with the requirements outlined in 21 CFR1271.250, 21CFR1271.290, Regulation Ethics committee (EC) 1394/2007, the Directive 2004/23/EC as well as the rules and principles of the European (EU) “Detailed guidelines on good clinical practice specific to advanced therapy medicinal products”. 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 Cell and Gene Therapies Unit Product Quality Department. A unique subject identifier will be used in order to maintain the chain of identity between the autologous leukapheresis material and the tisagenlecleucel batch, and the link between subject identity and unique subject identifier will be confirmed prior to infusion. The [Novartis Product Handling Manual for Clinical Trials: CAR-T Products] 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.

The investigator or designee must maintain an accurate record of the drug receipt logs and Drug Accountability Forms. Drug accountability will be reviewed by the field monitor during site visits and prior to the completion of the study. At study close-out, and, as appropriate during the course of the study, the investigator will return a copy of the completed drug accountability forms to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

6.6.2 Recommended treatment of adverse events

Subjects infused with tisagenlecleucel are at risk of developing a number of AE that are related either to tisagenlecleucel itself, other therapies (eg: immunochemotherapy) and conditions concurrent with the subject's primary disease. Following tisagenlecleucel infusion, subjects 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.

6.6.2.1 Cytokine release syndrome (CRS)

Ensure that at least two doses tocilizumab per subject are available on site prior to infusion of tisagenlecleucel. Hospitals should have timely access to additional doses of tocilizumab. Supportive care, tocilizumab, and corticosteroids have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most subjects. For further information relating to the administration of tocilizumab in the treatment and management of CRS symptoms, including warnings, precautions, and relevant ADRs, please refer to local prescribing information [Actemra USPI].

Identify cytokine release syndrome (CRS) based on clinical presentation (see Section 4.5.1.1). 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 subjects for signs or symptoms of CRS for at least 4 weeks after treatment with tisagenlecleucel. Counsel subjects to seek immediate medical attention should signs or symptoms of CRS occur at any time. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.

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

A detailed treatment algorithm for the management of CRS (Lee et al 2014) is presented below in Table 6-1 and Table 6-2. The CRS management algorithm is a guideline and the investigator may use discretion or modify the treatment approach as needed for an individual subject.

If requested by HA or EC/IRB or based on local practice, more frequent monitoring assessment and/or hospitalization can be implemented by the physicians.

Subjects will be required to remain proximal to the treating site for the first 4 weeks.

Table 6-1 CRS management

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Mild symptoms requiring symptomatic treatment only e.g. low fever, fatigue, anorexia, etc.	Exclude other causes (e.g. infection) and treat specific symptoms with e.g. antipyretics, anti-emetics, anti-analgesics, etc.	Not applicable	Not applicable

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
	If neutropenic, administer antibiotics per local guidelines		
Symptoms requiring moderate intervention: - high fever - hypoxia - mild hypotension	Antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed.	If no improvement after symptomatic treatment administer tocilizumab i.v. over 1 hour: - 8 mg/kg (max. 800 mg) if body weight ≥ 30 kg - 12 mg/kg if body weight <30 kg If no improvement, repeat every 8 hours (max total of 4 doses)*	If no improvement within 12-18 hours of tocilizumab, administer a daily dose of 2 mg/kg i.v. methylprednisolone (or equivalent) until vasopressor and oxygen no longer need, then taper.*
Symptoms requiring aggressive intervention: -hypoxia requiring high-flow oxygen supplementation or - hypotension requiring high-dose or multiple vasopressors	High-flow oxygen Intravenous fluids and high-dose vasopressor/s Treat other organ toxicities as per local guidelines		
Life-threatening symptoms: - hemodynamic instability despite i.v. fluids and vasopressors - worsening respiratory distress - rapid clinical deterioration	Mechanical ventilation Intravenous fluids and high-dose vasopressor/s Treat other organ toxicities as per local guidelines		

* If no improvement after tocilizumab and steroids, consider other anti-cytokine and anti-T-cell therapies. These therapies may include siltuximab (11 mg/kg i.v. over 1 hour), high doses of steroids (e.g. high dose methylprednisolone or equivalent steroid dose according to local ICU practice) cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab.

Table 6-2 Definition of high dose vasopressors

Vasopressor	Dose to be given for ≥ 3 hours	
	Weight-based dosing[¥]	Flat dosing[§]
Norepinephrine monotherapy	≥ 0.20 mcg/kg/min	≥ 20 mcg/min
Dopamine monotherapy	≥ 10 mcg/kg/min	≥ 1000 mcg/min
Phenylephrine monotherapy	≥ 2 mcg/kg/min	≥ 200 mcg/min
Epinephrine monotherapy	≥ 0.1 mcg/kg/min	≥ 10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 0.1 mcg/kg/min[a]	Vasopressin + NE ≥ 10 mcg/min[b]
If on combination vasopressors (not vasopressin)	NE of ≥ 0.2 mcg/kg/min[a]	NE of ≥ 20 mcg/min[b]

[§]If institutional practice is to use flat dosing.

[¥]Weight-based dosing was extrapolated by dividing the flat dosing of a vasopressor by 100.

Vasopressin and Septic Shock Trial (VASST) norepinephrine equivalent equation:

[redacted]

[a]NE dose (weight-based dosing) = [norepinephrine (mcg/kg/minute)] + [dopamine (mcg/kg/minute) / 2] + [epinephrine (mcg/kg/minute)] + [phenylephrine (mcg/kg/minute) / 10] [b]NE dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10]

Source: Adapted from Lee et al 2014, Lee et al 2015, Russell et al 2008, Porter et al 2015 and Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric, dated 30-Jan-2018.

Other anti-cytokine therapies may also be considered upon their availability, if the subject does not respond to tocilizumab. If the subject 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 4.5.1.1. Cases of transient left ventricular dysfunction, as assessed by ECHO, have been reported in some subjects 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.

As the time-course and rapidity of CRS development varies among subjects, additional unscheduled blood samples may be collected as needed, if clinically feasible. Frequent monitoring of serum CRP, ferritin and cytokines should be considered during the clinical course of CRS of any severity (eg: 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 ferritin, CRP and serum cytokine levels should NOT be used for clinical management decisions related to the treatment of CRS.

6.6.2.2 Neurological adverse events (early or late)

Neurologic events, primarily reflective of encephalopathy and delirium, may occur after tisagenlecleucel infusion. These present clinically as signs and symptoms of varying severity such as confusion, disorientation, agitation, aphasia, somnolence and tremors. In severe cases seizures, motor weakness, incontinence, impaired consciousness, increased intracranial pressure, and cerebral edema may be concurrent to, following the resolution or in the absence of CRS. Subjects should be monitored for neurologic events, diagnostically worked-up and managed depending on the underlying pathophysiology and in accordance to local standard of care.

Evaluation:

- Thorough neurological examination, with frequent monitoring and determination of CTCAE grading as well as ASTCT Consensus ICANS Grading (Table 4-4).
- Diagnostic work up to evaluate potential secondary causes:
  - Brain imaging (CT scan and/or MRI): to exclude intracranial hemorrhage, disease relapse, evidence suggestive of infection or cerebral edema.
  - Lumbar puncture for CSF evaluation, if clinically indicated

[redacted]

- Chemistry laboratory testing
- Electroencephalogram (EEG)

Management:

- If the neurological event is concurrent with CRS refer to CRS algorithm table for treatment recommendation (Table 6-1).
- Consider anti-seizure medications (eg: Levetiracetam) for patient at high risk (prior history of seizure) or administer in the presence of seizure.
- For encephalopathy, delirium or associated events: appropriate treatment and supportive care should be implemented as per local standard of care. In worsening events, consider a short course of steroids (Neelapu et al 2018, Teachey et al 2018).

6.6.2.3 Hypersensitivity including acute infusion reactions

Subjects should be monitored for signs and symptoms of hypersensitivity following initiation of tisagenlecleucel infusion and treated appropriately. Tisagenlecleucel is contraindicated in subjects 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 subjects 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.

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. Subjects should be evaluated and carefully monitored until complete resolution of signs and symptoms.

6.6.2.4 Tumor lysis syndrome (TLS)

Subjects 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, subjects 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 (eg: febuxostat), and increased oral/i.v. hydration prior to lymphodepleting chemotherapy and tisagenlecleucel infusion should be given in subjects 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)

[redacted]

- **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 (eg: 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.

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).

6.6.2.5 Infections

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

Subjects 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 (eg: 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 6 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 subjects 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.

6.6.2.6 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 subject should be evaluated for infection (Section 4.5.1.5) and CRS (Section 4.5.1.1) and managed appropriately with fluids, antibiotics, and supportive care, if applicable.

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

6.6.2.7 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. Immunoglobulin levels in newborns of mothers treated with tisagenlecleucel should also be assessed and managed as per standard of care.

6.6.2.8 Hematopoietic cytopenias lasting greater than or equal to 28 days

Myeloid growth factors, particularly GM-CSF, have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.

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.

6.6.2.9 Replication competent lentivirus (RCL) production

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

- Intensive Follow-up of the subject 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

[redacted]

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

If uncontrolled T-cell proliferation occurs (eg: expansion of T cells in the absence of CD19 antigen), subjects 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.

6.6.2.11 Graft versus host disease (GVHD)

Graft versus host disease can be severe but can be controlled with steroids and other immunosuppressants as per local standard of care.

6.7 Preparation and dispensation

Manufacturing of tisagenlecleucel cells will occur at the Novartis manufacturing facilities in Morris Plains, NJ, USA, Fraunhofer Institute, Leipzig, Germany or at contract manufacturing organizations (CMOs).

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 [Novartis Leukapheresis, Cryopreservation, and Scheduling Manual for Clinical Trials: CAR-T] and the [Novartis Product Handling Manual for Clinical Trials: CAR-T Products].

6.7.1 Handling of study treatment

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.

A study physician MUST evaluate the subject just prior to infusion to ensure the subject meets tisagenlecleucel infusion criteria. Coordination of the timing of thaw of tisagenlecleucel product and infusion will be done. The tisagenlecleucel product will be thawed using either a water bath or dry thaw method. Prior to infusion, confirmation of the subject's identity with the subject identifiers on the infusion bag will be done. Once thawed, tisagenlecleucel product may be stored at room temperature (20°C to 25°C) and administered as an intravenous infusion within 30 minutes from thawing.

[redacted]

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 subject except for the medication number.

Tisagenlecleucel can be infused both in an inpatient or outpatient facility per investigator's discretion. Factors such as, but not limited to, subject's disease status and general health condition, proximity to infusion facility, and ability to monitor and report any post-infusion symptoms as advised by investigator or site personnel, should be considered in determining inpatient/outpatient infusion. Due to lack of experience in treating B-cell NHL in pediatric subjects with tisagenlecleucel, it is recommended to infuse subjects in an inpatient setting.

Trained study staff will administer the tisagenlecleucel infusion using precautions for immunosuppressed subjects. Protective isolation should follow institutional standards and policies. Emergency medical equipment should be available during the infusion in case the subject has a significant reaction to the infusion such as anaphylaxis or severe hypotension.

The tisagenlecleucel dose will be administered via a single intravenous infusion. Depending on the volume of the tisagenlecleucel product, it will be given either as an i.v. infusion through a latex free i.v. tubing WITHOUT a leukocyte filter (approximately 10-20 mL per minute adjusted as appropriate for smaller children and smaller volumes) or as an i.v. push via a syringe (for smaller volumes). It is recommended that the infusion/i.v. push be completed within 30 minutes of thawing the cryopreserved product in order to preserve maximum cell viability. 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 repeated at 2 hours. If vital signs are unsatisfactory and unstable, continue to monitor the subject until vital sign stabilization.

All used infusion supplies, including the infusion bag and tubing, must be disposed of according to local institutional standard operating procedures. For further details on product storage, preparation, thawing and administration, please refer to the specific guidance provided in the [Novartis Product Handling Manual for Clinical Trials: CAR-T Products].

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

Tisagenlecleucel disposal and destruction

Tisagenlecleucel cell product may require disposal for a variety of reasons, including but not limited to: 1) Mislabeled product; 2) Condition of patient prohibits infusion; and/or 3) Patient refuses infusion. Disposal of unused tisagenlecleucel product must be approved by Novartis study team. Upon Novartis approval, tisagenlecleucel may be disposed of according to local laws/ institutional SOP.

Any used infusion supplies, including the infusion bag(s) and tubing, must be disposed of according to local institutional standard operating procedures. Reconciliation of tisagenlecleucel cell product shipped, administered, and remaining, is performed by Novartis (or designee). All tisagenlecleucel cell product dispositions will be documented in the study files. At study close-out, and as appropriate during the course of the study, the investigator will

[redacted]

return a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

Please refer to the recent [Novartis Product Handling Manual for Clinical Trials: CAR-T Products].

6.7.2 Handling of additional treatment

Additional treatments will be handled according to local guidelines.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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 (eg: all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH Good clinical practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed 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 subject informed consent and should be discussed with the subject 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 (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential 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.

Male subjects 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.

[redacted]

8 Visit schedule and assessments

Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study by withdrawing consent for any reason should be scheduled within 2 weeks for a visit or as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

In each 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 subject's source documentation. The tables indicate which assessments produce data to be entered into the clinical database (X) or remain in source documents only (S) ("Category" column). No CRF will be used as a source document.

The following assessments will be performed as per the Assessment Schedule (Table 8-1):

[redacted]

Table 8-1 Assessment Schedule

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Obtain Informed Consent	X																				
Interactive Web Response System (IWRS)/Interactive Response Technology (IRT)	S	S; clinical eligibility and leukapheresis acceptance			S									S					S		S
Subject History																					
Demography	X																				
Inclusion/exclusion criteria	X																				
Medical History and Concomitant disease	X																				

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Diagnosis and extent of cancer at initial presentation	X																				
Prior antineoplastic therapy	X																				
Concomitant antineoplastic therapy	X	X	X																		
Donor chimerism (local; only if received prior allogeneic SCT or if unknown)	X																				
Cytogenetics (local lab)	X																				
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IVIG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Tumor tissue-lymph node/extranodal (archival paraffin blocks/slides or fresh tumor from biopsy/resection, for efficacy/biomarkers/PK assessments)	X													X; residual tumor biopsy if available							
						At relapse															
Tumor immunophenotyping See Section 8.1 for details	X					At relapse															
Physical assessments																					
Physical examination (PE); pregnancy assessment as applicable	S	S	S	S		S		S		S		S	S	S	S	S	S	S	S	S	S
Performance status assessment	X			X		X		X		X		X	X	X	X	X	X	X	X		X
Height	X			X									X	X	X	X	X	X	X	X	X

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Tanner staging (only for subjects <18 years old; stop once Tanner 5 is reached)	X														X		X		X	X	X
Weight	X		X	X		X		X		X		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ECHO/MUGA/ MRA	X																				
ECG	X				X																
Pulse oximetry	X				X																
Intervention																					
Leukapheresis	X																				
Lymphodepleting Chemotherapy			X																		
Tisagenlecleucel pre-infusion criteria				S	S																
Tisagenlecleucel infusion					X																

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Antineoplastic therapies after tisagenlecleucel infusion or study discontinuation						X As appropriate															
Laboratory assessments																					
Hematology (local lab)	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (local lab)	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local flow cytometry leukapheresis (fresh product)	X																				
Local lab tests of special interest in case of CRS (ferritin, CRP and coagulation factors)					X; During CRS only, refer to Section 6.6.2.1.																

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Pregnancy tests (serum test required at screening, pre-leukapheresis,pre-lymphodepletion, pre-infusion and at EOS; Urine test at other time points (local lab)) and menstrual status	S		S (within 24 hours prior to first dose)	S (within 24 hours prior to infusion)									S	S	S	S	S	S	S	S	S
Urinalysis (local lab)	S			S									S								
Viral serology (HIV, Hepatitis B & C testing (HCV) (local lab)	X (repeat Hepatitis and HIV serology if >8 weeks from infusion)																				

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Influenza A and B testing (local lab)				X (within 10 days prior to infusion)																	
Coagulation (PT, activated partial thromboplastin time (aPTT), INR, fibrinogen, D-dimer) (local lab)	X		X		X			X		X			X								
Serum immunoglobulin levels (IgG, IgA, IgM) (local lab)	X									X			X	X	X				X		X

Period		Pre-treatment			Treatment and Follow-up															
Visit Name	**Screening**	**Enrollment**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Follow-up (until EOS)**														
Day/Week/Month	**W-16 to W-1**	**W-12 to W-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±7d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±28d**	**M18 ±28d**	**M24 ±28d**	**Annual Follow-up**	**EOS**
Efficacy and disease assessments (Refer to Table 8-2, Appendix 1)																				
Local overall disease assessment	X		X after completion of bridging therapy										X (as clinically indicated)	X	X	X	X	X	X	X	X
CT/MRI - Neck, Chest, Abdomen, Pelvis	X (within 8 weeks prior to screening for eligibility)		X within 2 weeks prior to infusion										X (as clinically indicated)	X	X	X	X	X	X	X	X

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
PET-CT with contrast enhanced diagnostic CT/PET-MRI - Neck, Chest, Abdomen, Pelvis			X (if no CT/MRI available)			X As clinically indicated, if CT/MRI is not available															

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Bone marrow (BM) aspirate or biopsy (local)	X (within 8 weeks of screening)		X (if BM involvement at screening or as clinically indicated; within 2 weeks prior to infusion											X (if BM involvement at baseline OR as clinically indicated)	At the time of radiological CR/PR/MR/NR in subjects with bone marrow disease at baseline or as clinically indicated						

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Bone marrow (BM) aspirate or biopsy (local) for subjects with Burkitt Leukemia	X (within 8 weeks of screening)		X										X	X	X	X	X	At the time of radiological CR/PR/MR/NR or as clinically indicated			
CSF cytology (by lumbar puncture; local)	X						X As clinically indicated														

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	**Screening**	**Enrollment**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Follow-up (until EOS)**															
Day/Week/Month	**W-16 to W-1**	**W-12 to W-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±7d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±28d**	**M18 ±28d**	**M24 ±28d**	**Annual Follow-up**	**EOS**
CT/MRI Brain	X (within 8 weeks prior to screening as clinically indicated)		X (within 2 weeks prior to infusion as clinically indicated)		X As clinically indicated																
Color Photography (only in case of any skin lesions; with scale/ruler) (local)	X (within 8 weeks prior to screening)		X within 2 weeks prior to infusion										X (as clinically indicated)	X	X	X	X	X	X	X	X

[redacted]

Period		**Pre-treatment**			**Treatment and Follow-up**																
Visit Name	**Screening**	**Enrollment**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Follow-up (until EOS)**															
Day/Week/Month	**W-16 to W-1**	**W-12 to W-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±7d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±28d**	**M18 ±28d**	**M24 ±28d**	**Annual Follow-up**	**EOS**
Biomarker (central lab) and safety assessments																					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X; AE SI only	X
ICANS Consensus Scoring & CAPD/ICE score				X	At the first sign or symptom of neurologic toxicity, the ICANS grade should be determined (as part of or outside the scheduled physical examination). If the patient experiences suspected worsening of the event, the grade should be reassessed and the worst grade should be recorded.																
Immunogenicity, Humoral (serum)*		X (not required for subject ≤15 kg)	X							X (not required for subject ≤15 kg)			X	X	X (not required for subject ≤15 kg)		X (not required for subject ≤15 kg)	X (not required for subject ≤15 kg)	X (not required for subject ≤15 kg)		X (not required for subject ≤15 kg)
														At relapse							

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	**Screening**	**Enrollment**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Follow-up (until EOS)**															
Day/Week/Month	**W-16 to W-1**	**W-12 to W-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±7d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±28d**	**M18 ±28d**	**M24 ±28d**	**Annual Follow-up**	**EOS**
Immunogenicity, Cellular (Peripheral Blood)*		X (1 sample at enrollment/pre-chemotherapy)											X	X	X (not required for subject ≤15 kg)		X (not required for subject ≤15 kg)	X	X (not required for subject ≤15 kg)		X (not required for subject ≤15 kg
														At relapse							
Cytokines (serum)		X		X		X	X	X	X	X	X	X	X								
Serum (Rituximab) (if applicable)*				X																	
CRS assessments by peripheral blood (Tisagenlecleucel qPCR, serum biomarkers, anti-cytokine therapy)					X As clinically indicated dependent upon the presence and time-course of CRS and administration of anti-cytokine therapies. [redacted]																

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
[redacted]																					

Period		Pre-treatment			Treatment and Follow-up															
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)														
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Tisagenlecleucel Cellular Kinetics by qPCR (peripheral blood)*		X					X (not required for subject ≤15 kg)	X	X	X (not required for subject ≤15 kg)		X (not required for subject ≤15 kg)	X	X	X	X (not required for subject ≤15 kg)	X	X (not required for subject ≤15 kg)	X (not required for subject ≤15 kg)	X	X (not required for subject ≤15 kg)
														At relapse							
Tisagenlecleucel Cellular Kinetics by Flow cytometry (peripheral blood)*		X (1 sample at enrollment/pre-chemotherapy)						X	X (not required for subject ≤15 kg)	X (not required for subject ≤15 kg)	X (not required for subject ≤15 kg)		X	X	X	X (not required for subject ≤15 kg)	X (not required for subject ≤15 kg)	X (not required for subject ≤15 kg)			
														At relapse							

[redacted]

Period		Pre-treatment			Treatment and Follow-up																	
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)																
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS	
Tisagenlecleucel Cellular Kinetics by qPCR (bone marrow)*														X	At relapse or as clinically indicated: M6, M9, M12, M18 and M24 collections are recommended (only if disease present in bone marrow at baseline)							
Tisagenlecleucel Cellular Kinetics by Flow cytometry (bone marrow)*						X As clinically indicated																
Tisagenlecleucel Cellular Kinetics by qPCR in CSF*						X As clinically indicated																
Correlative studies (central lab)																						
Leukapheresis sample for correlative studies	X																					
Tisagenlecleucel cell product sample for correlative studies		X																				
Survival						X; Q3M ±28d until EOS																
	X				X																	

[redacted]

Period		Pre-treatment			Treatment and Follow-up																
Visit Name	Screening	Enrollment	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Follow-up (until EOS)															
Day/Week/Month	W-16 to W-1	W-12 to W-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±7d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±28d	M18 ±28d	M24 ±28d	Annual Follow-up	EOS
Disposition		X; EOS (post-infusion, all assessments required at M24 are expected to be completed)																			

X = assessment to be recorded in the clinical database or received electronically from a vendor

S = assessment to be recorded in the source documentation only

* For patients with poor clinical condition and/or low body weight, PK and immunogenicity sample should only be collected if it does not interfere with the medical management of the patient or does not put the patient at an unnecessary safety risk.

[redacted]

8.1 Screening

An IRB/EC approved informed consent form (ICF) must be signed before any study specific screening procedures. Screening assessments to determine eligibility should be performed as per the assessment schedule detailed in Table 8-1. Procedures performed prior to ICF as part of routine standard of care may be considered for eligibility, if performed within allowed windows outlined in this section of the protocol.

Screening procedure(s) that do not satisfy the eligibility criteria may be 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 eligibility criteria as specified in Section 5. Re-leukapheresis is also allowed in case the leukapheresis material is not accepted for manufacturing or if manufacturing has failed. In these cases, the subject may not have to re-consent, and the original subject identification (ID) number assigned by the investigator will be used.

Subjects who have signed an informed consent will be registered in the IRT system and undergo a routine lymphoma staging workup including all screening assessments outlined in Table 8-1.

The assessments below do not need to be repeated if performed in the context of the leukapheresis procedure or if performed as part of clinical routine prior to **4 weeks** of signing the ICF:

- Local flow cytometry leukapheresis
- Serum immunoglobulin levels (IgG, IgA, IgM)
- Donor Chimerism (within 3 months of screening, prior allogeneic SCT patients only, or if unknown)

Laboratory parameters or other screening parameters may be retested within the screening period for an individual subject.

In the event that the time between routine standard of care testing or initial screening assessment and the enrollment exceeds **8 weeks**, the following must be repeated:

- ECHO/MUGA/MRA
- Viral serology (HIV, HbsAg, HBsAb, HBcAb, hepatitis C virus (HCV)) ribonucleic acid (RNA). If HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines (see Appendix 2 for interpretation of Hepatitis B and Hepatitis C results)
- Performance status assessment
- Complete Blood Count with differential and Platelet Count, Chemistry Panel, Coagulation Panel
- Urinalysis
- Pregnancy Test (as applicable)

In the event that the time between routine standard of care testing or initial screening assessment and enrollment exceeds **12 weeks**, the below screening procedures must be repeated in addition to the above:

[redacted]

- Physical Examination (PE) including height, weight, vital signs, extramedullary disease assessment and CNS symptom assessment
- Pulse oximetry
- Imaging (CT/MRI or PET-CT or fluorodeoxyglucose 18F (FDG)-PET)
- CSF cytology as clinically indicated
- Bone marrow aspirate and/or biopsy (if clinically indicated or diagnosis of Burkitt leukemia)
- CNS Brain Imaging (CT/MRI) (if clinically indicated)

8.1.1 Subject demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.1.1.1 Demographics

The following demographic data will be collected:

- Age
- Gender
- Race
- Ethnicity

8.1.1.2 Baseline characteristics

The following baseline characteristics will be collected:

- Primary disease
- Medical history, concomitant conditions
- Prior medication
- Prognostic factors

8.1.2 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 possible manufacturing failure.

Once leukapheresis is collected, information on the subject's leukapheresis material including sample sentinel vials collected from leukapheresis (when available) will be sent to Novartis manufacturing separately or together with leukapheresis material. Final enrollment is defined as the point at which the subject meets all clinical inclusion/exclusion criteria, and the subject's leukapheresis material is received and accepted for manufacturing.

At the investigator's discretion and taking into consideration the subject's expected length of survival and the manufacturing process, additional leukapheresis collections may be performed. It is recommended not to exceed a maximum of two apheresis procedures/attempts within a 14

[redacted]

day window. It is at the investigator's discretion whether the subject should continue with the procedure or be rescheduled for an additional procedure/attempt.

Cryopreserved non-mobilized leukapheresis materials collected prior to study entry (historical) may be usable for tisagenlecleucel manufacturing if collected at a Novartis certified leukapheresis center and if the product is accepted for manufacturing. **Historical product collected prior to the last allogeneic SCT would not be accepted.**

For subjects who will undergo leukapheresis collection on study after signing ICF, specific recommended criteria must be met prior to the procedure. Please refer to the Leukapheresis Key Requirements within the most recent [Novartis Leukapheresis, Cryopreservation, and Scheduling Manual for Clinical Trials: CAR-T Product] for more detailed instructions on optimal timing of leukapheresis collection, prohibited concomitant drugs, and the recommended procurement, handling and shipment procedures of the leukapheresis samples to the designated manufacturing facility.

8.1.3 Re-screening

Re-screening is allowed, at the discretion of the investigator, for subjects who screen fail or discontinue from the study prior to infusion.

A new ICF must be signed if the investigator chooses to re-screen the subject, and the re-screened subject will be assigned a new subject ID. In such cases, a rescreening CRF must be filled in to ensure the subject's original ID can be linked to the subject's new ID. All required screening activities must be performed when the subject is re-screened for participation in the study. Once the number of subjects screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the subjects who screen failed will not be permitted to re-screen.

8.1.3.1 Information to be collected on screening failures

For subjects that fail screening, the following information will be captured on appropriate Case Report Form:

- Informed Consent Information
- Demography
- Inclusion/Exclusion Criteria
- Leukapheresis (if applicable)
- The reason for screen failure
- Adverse Events (if applicable) that meet reporting criteria in Appendix 3.
- Death (if applicable)
- Withdrawal of Consent (if applicable)

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

8.2 Enrollment

Following informed consent, information on the subject's leukapheresis material including sample sentinel vials collected from leukapheresis (when available) will be sent to Novartis

[redacted]

manufacturing facility separately or together with leukapheresis material. Enrollment is defined as the point at which a subject meets all clinical eligibility criteria and the subject's leukapheresis material is received and accepted for manufacturing. Once assigned, the Subject Number must not be re-used for any other subject. If a screened subject is not enrolled, the specific reason will be entered into the electronic Data Capture (EDC) system. Clinical eligibility (entered by site) and Enrollment upon product acceptance (entered by manufacturing facility) will be captured in the Interactive Response Technology (IRT) system. If a subject is re-screened, re-enrollment will also be recorded using the IRT system. If repeat screening procedures are needed after the initial clinical eligibility has been recorded in IRT, confirmation of new clinical eligibility must be captured in the IRT system. For detailed enrollment procedures related to the use of IRT, please refer to the [IRT User Manual].

8.3 Efficacy

Efficacy/Pharmacodynamics (PD) are measured per assessments described below.

8.3.1 Efficacy assessments

Eligibility will be determined by the local staging assessment by required radiology images and other assessments obtained during screening by the investigator. The decision regarding subject management will also remain with the local investigator.

Disease characterization at baseline and evaluation of efficacy during study rely on the following:

- Imaging
- Bone marrow biopsy or aspirate
- CSF cytology
- Physical exam findings/cytology/biopsy evaluation

Efficacy assessments will be performed locally at the site as indicated in Table 8-2, and as clinically indicated until relapse, disease progression, death, lost to Follow-up, withdrawal of consent or end of study. Efficacy evaluations will be based on the International Pediatric NHL Response Criteria (Sandlund et al 2015) as detailed in Appendix 1. The latest efficacy assessment after bridging therapy and prior to infusion will be used as baseline. Any imaging assessment obtained after infusion cannot be considered baseline/pre-infusion images.

Radiological imaging will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The results of the local evaluations will be used for primary and secondary analysis purposes. The local investigator's assessment will also be used for treatment decision making. **Central review of the imaging data may be performed if deemed necessary.**

Information regarding prior interventions (eg: radiotherapy), pre-existing radiographic findings that mimic metastatic disease at screening/baseline, physical exam finding (eg: skin lesions, etc.), cytology results and on-study procedures (eg: bone marrow biopsy, etc.) may be transmitted to the imaging CRO from the clinical database.

[redacted]

Table 8-2 Efficacy Assessment Collection Plan

Procedure	Screening	Baseline	During Treatment/Follow-up
CT or MRI Neck, Chest, Abdomen, Pelvis	Mandated to determine study eligibility and must be performed within 8 weeks prior to screening (allowed if part of clinical routine).	After the completion of bridging therapy and within 2 weeks prior to infusion (only if PET-CT with diagnostic CT or PET-MRI is not available)	At Month 3 (±14 days) (only if PET-CT with diagnostic CT or PET-MRI is not available); Mandated at Months 6, 9 (±14 days), Months 12, 18, 24 (±28 days) and annually thereafter or as clinically indicated until relapse, progression, death, lost to Follow-up or withdrawal of consent or EOS. As clinically indicated at Day 28 (±7 days); due to the mechanism of action of tisagenlecleucel, the Day 28 (±7 days) assessment should be interpreted in context of other clinical parameters that suggest true progression rather than pseudoprogression due to inflammatory changes and tumor swelling
PET-CT with contrast enhanced diagnostic CT or PET-MRI - Neck, Chest, Abdomen, Pelvis	N/A	Recommended; within 2 weeks prior to infusion of tisagenlecleucel product, if no CT/MRI available	Recommended; at Month 3 (±14 days) or as clinically indicted, if CT/MRI is not available Once CR is confirmed (prior to or after Month 3 (±14 days) PET imaging is not required (CT only)
Dedicated PET	N/A	Recommended; if no PET-CT or PET-MRI available within 2 weeks prior to infusion of tisagenlecleucel product	Recommended; at Month 3 (±14 days) (if no PET-CT/ PET-MRI available), or as clinically indicted. Once CR is confirmed (prior to or after Month 3 (±14 days) PET imaging is not required (CT only)
Bone marrow aspirate or biopsy	Mandated within 8 weeks prior to screening	Mandated if diagnosis of Burkitt leukemia, bone marrow involvement at screening, or as clinically indicated; done within 2 weeks prior to infusion	Mandated at Month 3 (±14 days) and at time of radiological CR/PR/MR/NR in subjects with baseline bone marrow disease and at other times as clinically indicated For Burkitt leukemia: Mandated at Day 28 (±7 days), Month 3 (±14 days), Month 6 (±14 days), Month 9 (±14 days) and Month 12 (±28 days) and then as clinically indicated.
CSF Cytology	Mandated	NA	As clinically indicated

[redacted]

Procedure	Screening	Baseline	During Treatment/Follow-up
CT/MRI Brain	As clinically indicated within 8 weeks prior to screening	If clinically indicated within 2 weeks prior to infusion	As clinically indicated
Color photography (with scale/ruler)	For any skin lesions present; within 8 weeks prior to screening	For any skin lesions present; within 2 weeks prior to infusion	If skin lesions were documented at baseline, follow same schedule as CT/MRI of Neck, Chest, Abdomen, Pelvis
Tumor biopsy (FFPE)	Mandated from the time of diagnosis and/or at recent relapse prior to study entry		Recommended at Month 3 (±14 days) and required at relapse
[redacted]			
Physical Exam	Mandated	Mandated	Mandated
Other Biopsy	As clinically indicated	As clinically indicated	As clinically indicated

8.3.1.1 Baseline imaging assessments

Imaging assessments are as described in Table 8-2 and should be performed at the time points specified. Imaging assessments will be performed at screening preferably within 4 weeks prior to tisagenlecleucel infusion and will be used to determine eligibility. Any imaging assessments already completed during the regular work-up of the subject within 8 weeks prior to the screening visit, including before signing the main study ICF, can be considered as the screening images for this study to determine eligibility. After completion of bridging therapy and within 2 weeks prior to tisagenlecleucel infusion, imaging will be repeated (see Table 8-2) to establish baseline disease status. Any imaging assessments obtained after infusion cannot be considered baseline images.

A PET-CT with diagnostic CT/PET-MRI (or PET-CT without diagnostic CT + dedicated diagnostic CT or dedicated PET when PET-CT with diagnostic CT/PET-MRI not available) is recommended to be performed within 2 weeks prior to the scheduled tisagenlecleucel infusion. One of the following scanning scenarios are to occur prior to infusion and on study when PET imaging may be obtained:

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

Refer to Appendix 1 for details regarding imaging requirements.

If a subject 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 chest (MRI of chest is not

[redacted]

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 neck, abdomen and pelvis should be performed.

A MRI or CT of the brain must be performed at screening/baseline as clinically indicated and must be repeated within 2 weeks prior to tisagenlecleucel infusion as clinically indicated. 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 at screening as a result of a physical exam these are to be documented via the efficacy criteria, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

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

Chest x-rays and ultrasound should not be used to measure tumor lesions.

8.3.1.2 Post-baseline imaging assessments

Imaging assessments as described in Table 8-2 should be performed at the time points specified preferably using the same imaging modality used at baseline. CT/MRI imaging assessments for response evaluation may be performed on day 28 (±7 days) as clinically indicated post tisagenlecleucel infusion and will be repeated at Months 3, 6, 9, (±14 days) and at Months 12, 18, 24 (±28 days) and yearly thereafter or as clinically indicated until disease progression, death, lost to Follow-up, withdrawal of consent or EOS. PET/CT imaging is recommended to be performed at Month 3 (±14 days). Assessments should be scheduled using the infusion date as the reference date (not the date of the previous tumor assessment).

Additional imaging assessments may be performed at any time during the study at the investigator's discretion for suspicion of PD or to support the efficacy evaluations for a subject, as necessary. 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 assessed under a single evaluation.

Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

For subjects who discontinue post-treatment phase for reasons other than documented disease progression, death, lost to Follow-up, or withdrawal of consent, tumor assessments must continue to be performed until documented disease progression (per investigator), death, lost to Follow-up, withdrawal of consent or EOS; every 3 months in the first year, every 6 months in the second year and annually thereafter.

[redacted]

All study imaging (including any protocol required off-schedule imaging studies) should be submitted to the designated imaging CRO for quality control.

8.3.2 Other efficacy assessments

Bone marrow biopsy and/or aspirate and CSF by lumbar puncture must be performed within 8 weeks prior to screening and bone marrow biopsy/aspirate must be repeated 2 weeks prior to tisagenlecleucel infusion if there is bone marrow involvement at screening. In subjects with bone marrow involvement at baseline, biopsy or aspirate (of adequate quality) should be obtained at the time of disease response by imaging to confirm a response of CR, NR, MR or PR.

Tumor biopsy and histological as well as any molecular disease characterization is performed locally at screening. [redacted] Tumor biopsy is also recommended by International Pediatric Lymphoma response criteria at Month 3 (±14 days) to confirm CR and is required at relapse, particularly if PET shows residual metabolically active tissue to rule out interference of CTL019 activity with PET results.

Physical Examination (PE) including extramedullary disease assessment and CNS symptoms assessment are performed at screening, pre-infusion (Day -1) and at scheduled visits post-infusion.

8.3.3 Appropriateness of efficacy assessments

CT/MRI are well established disease monitoring imaging methods in pediatric lymphomas even though PET-CT with diagnostic CT or PET-MRI is considered to have superior diagnostic accuracy compared to standard imaging methods in adult lymphoma. Subjects are exposed to higher doses of ionizing radiation with PET-CT with diagnostic CT, which is exacerbated by multiple imaging time points during efficacy assessments. Furthermore, even small doses of radiation exposure may pose increasing risk of secondary malignancies and this is more likely in children (Sandlund et al 2015). CT-MRI are therefore appropriate modalities for response assessments in these pediatric population. PET-CT with diagnostic CT is recommended with less frequency; at baseline and at Month 3 (±14 days) to confirm disease response.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section (Section 10.1).

Safety will be monitored by physical examination, vital signs, physical development, performance status, assessing immunogenicity against tisagenlecleucel, lab abnormalities as well as collecting adverse events at every visit.

[redacted]

Table 8-3 Physical Assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings which begin or worsen after informed consent and meet the definition of an Adverse Event must be recorded on the Adverse Event CRF page.
Vital signs	Vital signs include temperature, blood pressure, pulse measurements, respiratory rate, and pulse oxygen.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg)) will be measured via a consistent method at each assessment, when possible.

8.4.1 Tanner staging (only for subjects <18 years old)

Tanner staging for subjects less than 18 years of age will be updated semiannually until M24 visit and annually thereafter. If a subject is classified as Tanner Stage 5 at screening or at any point during the trial, no further Tanner staging will be required for the remainder of the trial. Female subject reproductive status (menstrual status and pregnancy information) will be updated at Months 3, 6, 9, 12, 18 and 24, then annually thereafter.

8.4.1.1 Males

Genitalia stages

Stage 1: Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.

Stage 2: The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin. There is also some reddening of the scrotal skin.

Stage 3: Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.

Stage 4: Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin.

Stage 5: Genitalia adult in size and shape. No further enlargement takes place after Stage 5 is reached.

Pubic hair stages

Stage 1: Pre-adolescent. The vellus over the pubes is not further developed than that over the abdominal wall, ie, no pubic hair.

[redacted]

Stage 2: Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly at the base of the penis.

Stage 3: Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5: Hair distribution is adult in quantity and type and is described in the inverse triangle. Hair can be spread to the medial surface of the thighs.

8.4.1.2 Females

Breast stages

Stage 1: Pre-adolescent; elevation of papilla only.

Stage 2: Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.

Stage 3: Further enlargement of breast and areola, with no separation of their contours.

Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

Pubic hair stages

Stage 1: Pre-adolescent; the vellus over the pubes is not further developed than that over the anterior abdominal wall, no pubic hair.

Stage 2. Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia.

Stage 3: Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs, but not up the linea alba or elsewhere above the base of the inverse triangle.

8.4.2 Performance status

Karnofsky or Lansky Performance status scale will be used as described in Table 8-4.

[redacted]

Table 8-4 Karnofsky/Lansky Performance Scales

Karnofsky Scale (age ≥16 years)		Lansky Scale (age <16 years)	
Able to carry on normal activity and to work; no special care needed.		Able to carry on normal activity; no special care is needed	
100	Normal no complaints; no evidence of disease	100	Fully active, normal
90	Able to carry on normal activity; minor signs or symptoms of disease	90	Minor restrictions with strenuous physical activity
80	Normal activity with effort; some signs or symptoms of disease	80	Active, but gets tired more quickly
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.		Mild to moderate restriction	
70	Cares for self; unable to carry on normal activity or to do active work	70	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance, but is able to care for most of his personal needs	60	Up and around, but minimal active play; keeps busy with quieter activities
50	Requires considerable assistance and frequent medical care	50	Lying around much of the day, but gets dressed; no active play; participates in all quite play and activities
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.		Moderate to severe restriction	
40	Disabled; requires special care and assistance	40	Mostly in bed; participates in quiet activities
30	Severely disabled; hospital admission is indicated although death not imminent	30	Stuck in bed; needs help even for quiet play
20	Very sick; hospital admission necessary; active supportive treatment necessary	20	Often sleeping; play is entirely limited to very passive activities
10	Moribund; fatal processes progressing rapidly	10	Does not play nor get out of bed
0	Dead	0	Unresponsive

8.4.3 Laboratory evaluations

Screening and other laboratory assessments will be performed according to Table 8-1, Table 8-5 and Table 8-6. Additional assessments should be performed between visits as clinically required to follow AEs or tisagenlecleucel expected events and for detailed modified data capture for inpatient/in hospital events. For all laboratory assessments and electrocardiogram (ECG) that occur on Day 1, these should be performed prior to tisagenlecleucel infusion unless indicated otherwise.

The Investigator will evaluate the clinical significance of each applicable laboratory value outside of the reference range. This decision shall be based upon the nature and degree of the observed abnormality. Values which are considered clinically significant and/or study related to tisagenlecleucel will be noted. The Investigator may choose to repeat any abnormal result, in order to rule out laboratory error.

[redacted]

With respect to laboratory assessments listed within this protocol, please refer to the [Laboratory Manual] for more detailed instructions for the collection, handling, and shipment of PK and biomarker samples.

Table 8-5 Laboratory Assessments (local)

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin Concentration (MCHC), MCV (Mean Corpuscular Volume), Platelets, Red blood cells, White blood cells with complete differential (Basophils, Eosinophils, Lymphocytes, Atypical Lymphocytes, Monocytes, Neutrophils, Lymphoblasts, and Other)
Chemistry	Glucose (fasting or non-fasting), Blood Urea Nitrogen (BUN) or Urea, Creatinine, Sodium, Potassium, Calcium, Magnesium, Phosphorus, Chloride, Total Protein, Albumin, Bilirubin (total and direct), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Lactate Dehydrogenase (LDH), Ferritin, C-reactive Protein (CRP) and Uric Acid.
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocyte esterases, Nitrite, pH, Protein, Specific Gravity) If macroscopic panel is abnormal then perform microscopic panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR), activated Partial thromboplastin time (aPTT), fibrinogen, and D-dimer
Viral Serology	Rapid Influenza A & B, Hepatitis C Virus (HCV) RNA qualitative test or antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HbcAb) (anti-HBc), Hepatitis B surface antibody (anti-HBs), HIV (if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines)
CSF	White Blood Cells, Presence or absence of lymphoblasts, Red Blood cells, Glucose, Protein
Additional tests	Serum immunoglobulin levels (IgG, IgA, IgM), peripheral blood, donor chimerism (prior allogeneic SCT subjects only, or if unknown), bone marrow morphologic blast cell counts, flow cytometry on leukapheresis product
Pregnancy Test	Serum/Urine pregnancy test (refer to Table 8-1). Pregnancy test performed at screening, within 24 hours prior to leukapheresis, lymphodepleting chemotherapy, and tisagenlecleucel infusion and at EOS.

[redacted]

Table 8-6 Laboratory Assessments (central)

Test Category	Test Name
Flow cytometry (Screening and at relapse)	B cells, tumor cell immunophenotyping, CD19 assessment
Tumor clonal typing	Deep sequencing (peripheral blood and bone marrow aspirate)
Tisagenlecleucel assessments [redacted]	Tisagenlecleucel cellular kinetics by qPCR and/or flow cytometry (peripheral blood and bone marrow aspirate), [redacted]
Cytokines	Cytokine panel including IL-6, IL-6R, IL-10, TNF-α, IFN-γ (peripheral blood, CSF)
RCL (VSV-G)	Vesicular Stomatitis Virus Glycoprotein (VSV-G) qPCR (peripheral blood)
Immunogenicity	Prevalence and Incidence of immunogenicity against tisagenlecleucel (peripheral blood and serum)
[redacted]	[redacted]

8.4.4 Cardiac assessments

8.4.4.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed and evaluated locally as described in Table 8-1.

- at screening
- Day 1 (pre-infusion)

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF page.

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

8.4.4.2 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 subject 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.

8.4.5 Pregnancy

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,

[redacted]

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 women of child-bearing potential will have pregnancy testing. A pregnancy test must be performed within 24 hours prior to leukapheresis, lymphodepletion, and tisagenlecleucel infusion and at EOS. Serum pregnancy tests are required during screening (prior to lymphodepleting chemotherapy, serum/urine pregnancy test is acceptable) until prior to the tisagenlecleucel infusion and at EOS. Following tisagenlecleucel infusion, women of child-bearing potential will have serum or urine pregnancy tests performed (either at their scheduled visits or at-home using a urine pregnancy test kit provided) monthly up to Month 12 **and** until CAR-T cells are no longer present by qPCR on two consecutive tests. Additional pregnancy testing might be performed if requested by local requirements. For details on the frequency of pregnancy testing please refer to Table 8-1.

For all pregnancy tests performed at home, the site personnel will Follow-up with the subject via telephone call to collect the date and the test results and document the information in the subject's source documents.

Every effort must be made for the women of child bearing potential to return to the site for the final serum pregnancy test at the EOS. However, if the subject is unable to return to the site, then the subject will administer a urine pregnancy test at home using a kit 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 as per Section 10.1.6.

To ensure subject safety, each pregnancy occurring once the subject has been infused with tisagenlecleucel 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.

For monitoring and management of immunoglobulin levels in newborns of mothers treated with tisagenlecleucel see Section 6.6.2.7.

Pregnancy should be recorded on a Clinical Trial Pregnancy Report Form and reported by the investigator to the oncology 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 for any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

[redacted]

8.4.6 Other safety evaluations

For details regarding biomarker and PK evaluations to assess safety, please refer to Section 8.5.

8.4.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

Humoral immunogenicity to tisagenlecleucel and detectable RCL will be assessed as described Table 8-1.

8.5.1 Pharmacokinetics

For patients with poor clinical condition and/or low body weight, blood samples for PK and immunogenicity analysis should only be collected if an additional blood sampling does not result in an important concern such as interference with the medical management or clinical risk for the patient.

PK samples will be collected at the visits defined in the assessment schedule. Follow instructions outlined in the [Laboratory Manual] regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects.

Tisagenlecleucel PK and cellular kinetics will be used interchangeably throughout the protocol.

[redacted]

Table 8-7 Tisagenlecleucel pharmacokinetics by qPCR in peripheral blood collection log

Treatment Period or Cycle	Day	Scheduled Time Point*	Dose Reference ID	PK1 Sample No.	Sample Volume**
1	W-12 to D-1 Enrollment/Pre-Chemotherapy		101	901	3 mL
1	D4±1d	D4	101	902	3 mL
1	D7±1d	D7§	101	903	3 mL
1	D11 ±1d	D11§	101	904	3 mL
1	D14±3d	D14	101	905	3 mL
1	D21±3d	D21	101	906	3 mL
1	D28±7d	D28§	101	907	3 mL
1	M3±14d	M3§	101	908	3 mL
1	M6±14d	M6§	101	909	3 mL
1	M9±14d	M9	101	910	3 mL
1	M12±28d	M12§	101	911	3 mL
1	M18±28d	M18	101	912	3 mL
1	M24±28d	M24§	101	913	3 mL
1	M36±28d	M36	101	914	3 mL
1	M48±28d	M48	101	915	3 mL
1	Unscheduled (PK samples related to CRS)***		101	1001	3 mL
1	Unscheduled (PK samples at relapse)****		101	2001	3 mL
1	Unscheduled (PK samples related to safety events)		101	3001	3 mL

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

** All subject sample volumes subject to adjustment for size and subject condition.

*** Additional unscheduled samples may be collected as needed dependent upon individual subject differences in the clinical time-course of CRS and administration of anti-cytokine therapy, if clinically feasible. Unscheduled PK sample collections related to CRS will cease once PK sample collections related to anti-cytokine therapy commence, if applicable.

**** In the event subject relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample

Note: Tumor clonal typing by deep sequencing analysis (peripheral blood) is performed from these same samples. RCL by VSV-G qPCR is performed at the relevant time points using DNA extracted from these samples.

§ for subjects ≤15 kg body weight, only these marked samples will be collected

Table 8-8 Tisagenlecleucel pharmacokinetics by flow cytometry in peripheral blood collection

Treatment Period or Cycle	Day	Scheduled Time Point*	Dose Reference ID	PK2 Sample No.	Sample Volume
1	W-12 to D-1 Enrollment/Pre-Chemotherapy	Pre-dose	101	201	2 mL
1	D7±1d	D7§	101	202	2 mL
1	D11±1d	D11	101	203	2 mL
1	D14±3d	D14	101	204	2 mL
1	D17±3d	D17	101	205	2 mL
1	D28±7d	D28§	101	206	2 mL
1	M3±14d	M3§	101	207	2 mL
1	M6±14d	M6§	101	208	2 mL
1	M9±14d	M9	101	209	2 mL
1	M12±28d	M12	101	210	2 mL
1	M18±28d	M18	101	211	2 mL
1	Unscheduled (PK samples related to CRS)**		101	4001	2 mL
1	Unscheduled (PK sample at relapse)***		101	5001	2 mL

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

** Additional unscheduled samples may be collected as needed dependent upon individual subject differences in the clinical time-course of CRS, if clinically feasible.

*** In the event subject relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample

§ for subjects ≤15 kg body weight, only these marked samples will be collected

[redacted]

Table 8-9 Tisagenlecleucel pharmacokinetics by qPCR in bone marrow aspirate collection log

Treatment Period or Cycle	Day	Scheduled Time Point*	Dose Reference ID	PK3 Sample No.	Sample Volume**
1	M3±14d	M3	101	302	2 mL
1	Unscheduled (PK sample at relapse)		101	7001	2 mL
1	Unscheduled (eg: related to safety events)		101	8001	2 mL

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

** All subject sample volumes subject to adjustment for size and subject condition.

Note: Tumor clonal typing by deep sequencing analysis (bone marrow aspirate) may be performed from these same samples.

Table 8-10 Tisagenlecleucel pharmacokinetics by flow cytometry in bone marrow aspirate collection log

Treatment Period or Cycle	Day	Scheduled Time Point*	Dose Reference ID	PK4 Sample No.	Sample Volume**
OBJ					
1	Unscheduled (PK sample at relapse)		101	9001	2 mL
1	Unscheduled (eg: related to safety events)		101	1101	2 mL /collection

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

** All subject sample volumes subject to adjustment for size and subject condition.

Table 8-11 Tisagenlecleucel pharmacokinetics by qPCR in CSF collection log

Treatment Period or Cycle	Day	Scheduled Time Point*	Dose Reference ID	PK5 Sample No.	Sample Volume
1	Unscheduled		101	2101	4-6 mL

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

Table 8-12 Immunogenicity (humoral) serum sample collection log

Treatment Period or Cycle	Day	Scheduled Time Point*	Dose Reference ID	IG1 Sample No.	Sample Volume
1	W-12 to D-1 Enrollment/Pre-Chemotherapy	Pre-dose	101	601	3 mL
1	D-14 to D-2 Lymphodepleting chemotherapy	Pre-dose§	101	602	
1	D14±3d§	D14	101	603	3 mL
1	D28±7d	D28§	101	604	3 mL
1	M3±14d	M3§	101	605	3 mL
1	M6±14d	M6	101	606	3 mL
1	M12±28d	M12	101	607	3 mL
1	M18±28d	M18	101	608	3 mL
1	M24±28d	M24	101	609	3 mL
1	Unscheduled (at relapse)**		101	3101	3 mL
1	Unscheduled (eg: related to safety events)		101	4101	3 mL /collection

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

** In the event subject relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK samples

§ for subjects ≤15 kg body weight, only these marked samples will be collected

Table 8-13 Immunogenicity (cellular) peripheral blood sample collection log

Treatment Period or Cycle	Day	Scheduled Time Point*	Dose Reference ID	IG2 Sample No.	Sample Volume**
1	W-12 to D-1 Enrollment/Pre-Chemotherapy	Pre-dose§	101	701	10 mL
1	D28±7d	D28§	101	702	10 mL
1	M3±14d	M3§	101	703	10 mL
1	M6±14d	M6	101	704	10 mL
1	M12±28d	M12	101	705	10 mL
1	M18±28d	M18§	101	706	10 mL
1	M24±28d	M24	101	707	10 mL
1	Unscheduled (at relapse)**		101	5101	10 mL
1	Unscheduled (eg: related to safety events)		101	6101	10 mL /collection

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

** All subject sample volumes subject to adjustment for size and subject condition.

[redacted]

*** In the event subject relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK sample.

§ for subjects ≤15 kg body weight, only these marked samples will be collected

[redacted]

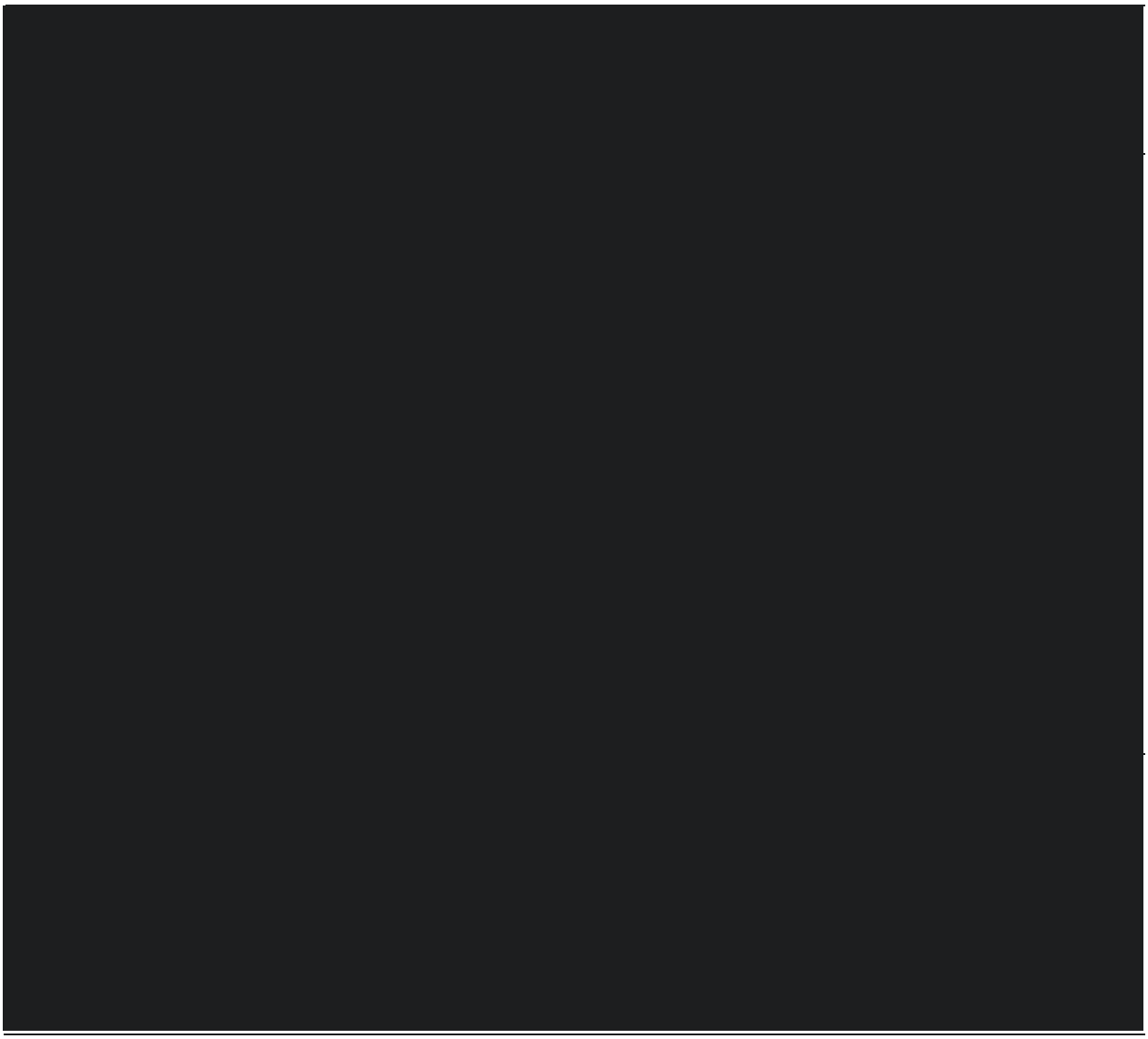


Table 8-15 Rituximab PK

Cycle	Day*	Scheduled time point relative to time post CTL019 dosing	Dose Reference ID	PK7 Sample No. (Rituximab)	Blood Volume (mL)
1	D-1	Pre-dose	101	801	3

* Day and scheduled time point are relative to the date of CTL019 infusion

8.5.1.1 Analytical method

The assays to be utilized for various PK/biomarker assessments include qPCR assay to detect CTL019/4-1BB+ cells (transgene copies/microgram DNA) in peripheral blood and other tissues and flow cytometric analysis to detect tisagenlecleucel positive cells. Details regarding collection and processing of the samples used in these assays will be provided in the [Central Laboratory Manual].

8.5.1.2 Pharmacokinetic blood collection and handling

For patients with poor clinical condition and/or low body weight, blood samples for PK and immunogenicity analysis should only be collected if an additional blood sampling does not result in an important concern such as interference with the medical management or clinical risk for the patient.

PK samples will be collected at the visits defined in the assessment schedule. Refer to the [Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples. See the potential use of residual samples for more information.

8.5.2 Biomarkers

Sample(s) will be collected at the time point(s) defined in the assessment schedule.

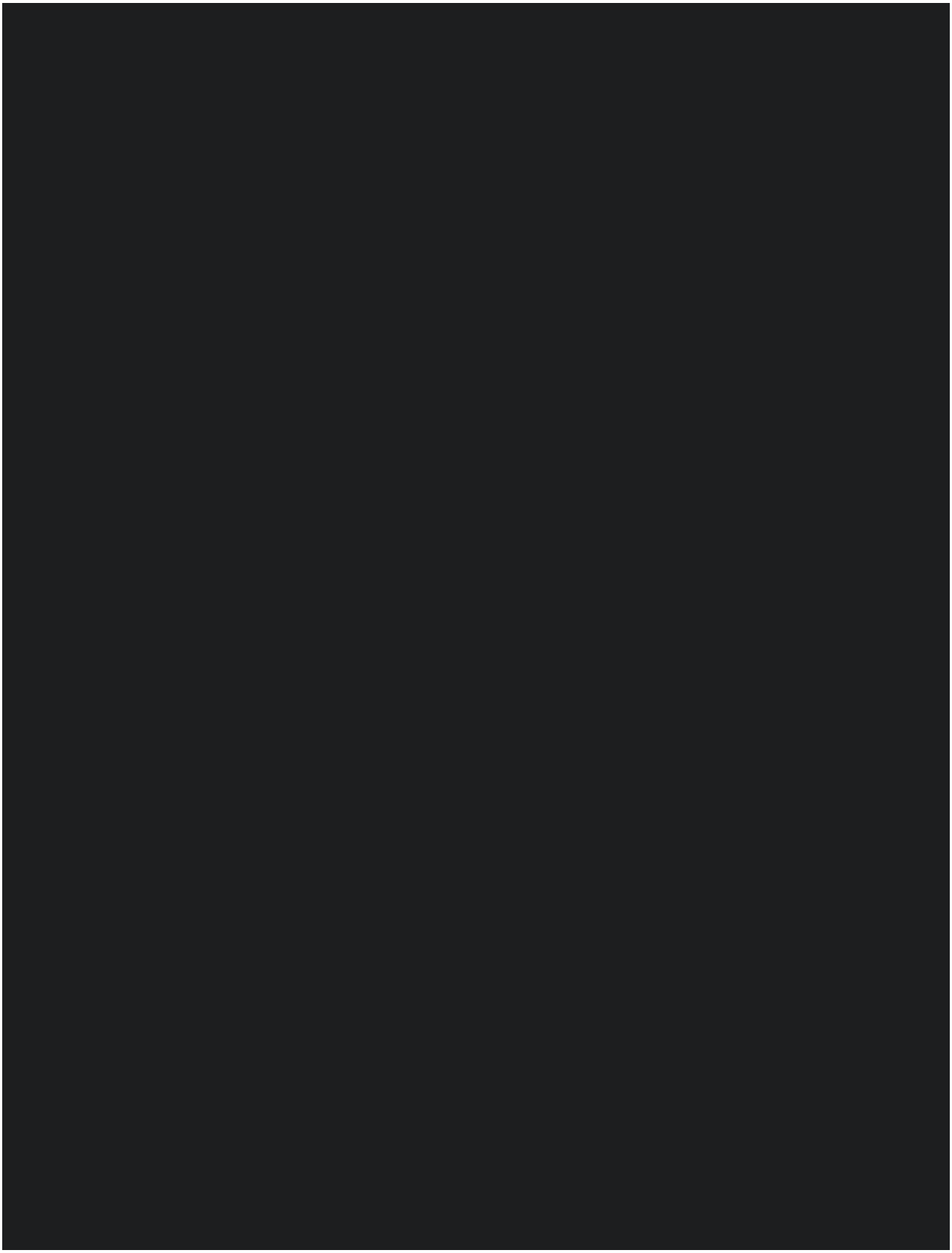
Follow instructions for sample collection, numbering, processing and shipment provided in the [Laboratory manual].

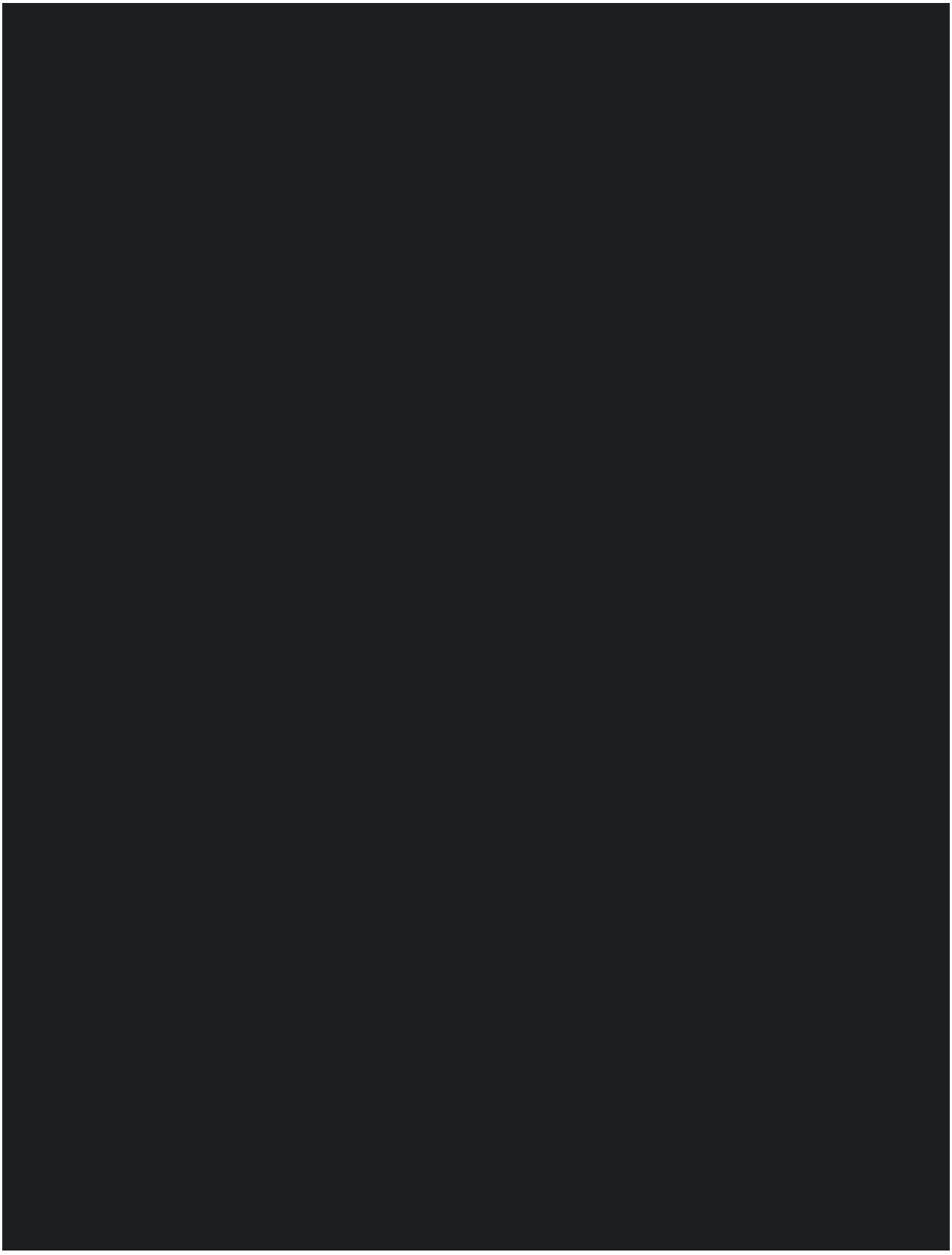
Biomarker analyses will focus on:

[redacted]

2. Correlation analysis of biomarker measurements performed pre- and post-infusion with key outcomes of efficacy and safety such as CRS

[redacted]





8.5.3 Imaging

The methods for assessment and recording are specified in Table 8-2 and Appendix 1.

8.5.4 Other Assessments

No additional tests will be performed on subjects entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study, prior to tisagenlecleucel infusion

Study treatment (eg: tisagenlecleucel infusion, lymphodepletion, and other therapies used in combination with tisagenlecleucel) may be discontinued if, in the investigator's opinion, its continuation would be detrimental to the patient's safety.

Subjects who discontinue before tisagenlecleucel infusion should NOT be considered discontinued from the study before they return for the End-of-Study (EOS) assessments, as appropriate. The EOS assessment visit should be completed within 2 weeks of the decision to discontinue the study. If they fail to return for these assessments, every effort (eg: telephone, email, or letter) should be made to contact them.

The investigator must also contact the IRT to register the subject's end of study.

Study treatment must be discontinued under the following circumstances:

- Death
- Subject/guardian/investigator decision
- Disease progression
- Pregnancy
- Use of prohibited treatment, against recommendations in the prohibited treatment Section 6.2.2.
- Any situation in which study participation might result in a safety risk to the subject
- Adverse events or any laboratory abnormalities that in the judgment of the investigator, prevents the subject from continuing participation in the study
- Manufacturing failure

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of the study treatment and record this information.

If a manufacturing failure occurs, the investigator may decide to repeat the leukapheresis for re-manufacturing. The clinical and operational aspects in case of manufacturing failures are described in protocol section 8.1. The bridging and patient stabilization treatment administered between the screening and the tisagenlecleucel infusion are described in Section 6.1 and Section 6.2.

[redacted]

If there is no additional cryopreserved material from the original leukapheresis collection to be sent, then, at the investigator's discretion and taking into consideration the subject's expected length of survival and the manufacturing process, additional leukapheresis collections may be performed. It is recommended not to exceed a maximum of two apheresis procedures/attempts within a 14 day window. In these cases, the subject may not have to re consent, and the original subject identification (ID) number assigned will be used.

Section 8.1 lists the procedures that would need to be repeated if the time between initial screening assessments and the enrollment exceeds 8 weeks or 12 weeks.

A subject who discontinues from the study prior to infusion can be re-screened. In this situation, a new ICF must be signed, and all required screening activities must be performed for participation in the study. In such cases, a rescreening CRF must be completed to ensure the subject's original ID can be linked to the subject's new ID.

A patient who had first manufacturing failure and the investigator's and/or subject's decision is not to pursue a second manufacturing, or if a subject fails two manufacturing attempts, the patient will be considered as enrolled in the trial and the discontinuation reason will be manufacturing failure. Those patients will be part of the enrolled analysis set.

9.1.2 Discontinuation from study, post-tisagenlecleucel infusion

Subjects who receive study treatment but decide to discontinue prematurely during Follow-up phase should NOT be considered to have completed the study (EOS) UNLESS the reason is death, lost to follow-up, or withdrawal of consent (see Section 9.1.3). In such cases, the investigator must contact the IRT to register the subject's EOS.

Subjects who decide to discontinue the follow-up phase post-infusion, prior to M24 visit for other reasons, **should return for the annual assessments indicated** in the Follow-up phase of assessment schedule (Table 8-1) until death, lost to Follow-up, withdrawal of consent, or EOS, whichever occurs first. In case of disease progression, no further imaging or response assessments are required.

Any new anti-cancer therapy treatment including HSCT must be recorded as part of the Follow-up assessments.

If the subject cannot or is unwilling to attend any visit(s) for any reason, the site staff should maintain contact (telephone, e-mail, letter, etc.) with the subject, or with a person pre-designated by the subject, **to obtain survival status once every 3 months** until death, lost to Follow-up, withdrawal of consent, or EOS (Section 9.2), whichever occurs first.

9.1.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject:

Does not want to participate in the study anymore

AND

Does not want any further visits or assessments

[redacted]

AND

Does not want any further study related contacts

AND

Novartis/sponsor will continue to keep and use collected study information (including any data resulting from the analysis of a subject'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.

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

No further assessments may be conducted, and the data that would have been collected at subsequent visits will be considered missing.

The investigator must contact the IRT to register the subject's end of study.

Further attempts to contact the subject 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 subject's study withdrawal should be made as detailed in the assessment Table 8-1.

After subject's withdrawal of consent, depending on the regional/country/local laws and requirements, Novartis may continue to retain and use all research results (data) and any biological samples that have already been collected for storage and future analyses.

9.1.4 Lost to Follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, eg: dates of telephone calls, registered letters, etc. A subject should not be considered as lost to Follow-up until due diligence has been completed or until the end of the study.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study

[redacted]

- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, the subject should be seen as soon as possible (within 2 weeks as indicated in Section 9.2) and the same assessments should be performed as described in Section 8 for a discontinued or withdrawn subject. 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 subject's interests. For subjects who have received the tisagenlecleucel infusion, a long term post-study Follow-up for lentiviral vector 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.

9.1.5.1 Criteria for stopping or pausing the study

The study will be stopped or paused, and health authorities notified if:

- Any subject develops detectable replication competent lentivirus (RCL) during the study
- The Sponsor, SC, or any regulatory body decides for any reason that subject safety may be compromised by continuing the study
- The Sponsor decides to discontinue the development of the intervention to be used in this study

The study may be paused while waiting for the notification of the Health Authorities and the SC for investigation and a possible protocol amendment if any subject experiences any of the following events within three weeks of the tisagenlecleucel cell infusion:

- Life-threatening (grade 4) toxicity that is unmanageable, unexpected, unrelated to preceding chemotherapy and considered attributable to protocol therapy. Identified safety risks expected to be associated with tisagenlecleucel include CRS, neurological events, hypersensitivity, TLS, infections, febrile neutropenia, prolonged depletion of normal B-cells cytopenias associated with hypo- or agammaglobulinemia, and prolonged hematopoietic cytopenias (see Section 4.5.1). In this setting, high fevers, hypotension, hypoxia, disseminated intravascular coagulation, encephalopathy (eg: lethargy, confusion, aphasia, seizure), ICU admission, dialysis and mechanical ventilation may occur. The expected risks can also result in grade 4 hepatotoxicity, nephrotoxicity and cardiotoxicity.
- Death suspected to be related to tisagenlecleucel therapy

9.2 End of study and long term Follow-up

The end of study (EOS) assessments for each subject is completed within 2 weeks of a subject's premature withdrawal of consent or when all infused and evaluable subjects with aggressive B-cell NHL have completed Month 24 evaluation or discontinued early. A final Clinical Study Report (CSR) will be produced once all subjects complete the study.

The primary efficacy and safety analysis will also be conducted when all evaluable subjects with aggressive r/r B-cell NHL have been infused and followed for at least 6 months from study

[redacted]

day 1 or discontinued early, as well as at least 50% of those infused subjects have a follow-up of at least 9 months. In addition, all subjects who complete the study will be enrolled in a separate LTFU protocol [CCTL019A2205B] at the time of EOS (a separate informed consent form will be provided for this protocol). Any subject who prematurely withdraws consent from the study will be given the option to enroll in the LTFU protocol at the time of withdrawal of consent from this study.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (eg: any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject 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 subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject 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.

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 10.1.2):

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with the exception of CRS, which will follow Section 6.6.2.1. 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 (ie, 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 subject.

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 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include treatment interruption or withdrawal.
6. Its outcome, ie, its recovery status or whether it was fatal.

If the event worsens, the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 AEs only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF 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 eCRF.

Adverse events (including laboratory 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.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (eg: 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.

Adverse events separate from the progression of malignancy (eg: 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 [Tisagenlecleucel Investigator's Brochure].

Abnormal laboratory values or test results constitute AEs 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 subjects with the underlying disease.

Detailed AE reporting requirements during the periods of screening, pre-treatment, treatment, follow-up and post-treatment are outlined in Table 16-7.

[redacted]

Detailed information regarding CRS adverse events (e.g. oxygen requirements, vasopressor usage) will also be collected to allow for assessment using alternative CRS grading scales (e.g. Lee et al 2019).

10.1.2 Serious adverse events

An 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 subject 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, unless hospitalization is for:
- 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 subject'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, e.g.: defined as an event that jeopardizes the subject 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 subject 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 (secondary malignancies, not disease progression of the study indication) will be assessed as serious under "medically significant".

Progression of the underlying malignancy with fatal outcome must be reported as a SAE within 24 hours of awareness, if the following criteria are met:

- Death within 30 days after tisagenlecleucel infusion, irrespective of causality to tisagenlecleucel
- Deaths beyond 30 days after tisagnelecleucel infusion, if there is at least a possible causality to tisagenlecleucel

[redacted]

Non-fatal disease progression should not be reported as AE.

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.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject 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. Additional SAE reporting requirements, including those for the periods of screening, pre-treatment, Follow-up and post-treatment, are also outlined in Appendix 3. 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 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.

For subjects who sign the main study ICF, SAE collection starts at time of main study informed consent whether the subject is a screen failure or not.

10.1.4 Adverse events of special reporting requirements

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

10.1.5 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.

10.1.6 Pregnancy reporting

To ensure subject 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

[redacted]

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 should be recorded and reported by the investigator on the Clinical Trial Pregnancy Report Form 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 on the SAE Report Form.

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 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.

10.1.7 Reporting of study treatment errors including misuse

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

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

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 10-1 Guidance for capturing the study treatment errors

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.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject 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 AE/SAE):

[redacted]

- 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 16-9 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-9 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 16-10. Repeat liver chemistry tests (ALT, AST, TBIL, ALB, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF
  If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough Follow-up of the liver event, which can include the following based on investigator's discretion:
  - 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, 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.

10.2.2 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, urinary tract infection (UTI), extreme exercise, or trauma)

Renal event findings must be confirmed 24-48 hours after the first assessment.

Every renal laboratory trigger or renal event as defined in Table 16-11 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 5.

10.2.3 Follow-up of secondary malignancy

For subjects treated with tisagenlecleucel, treating physicians/health care providers should contact Novartis if the subject develops a secondary malignancy. Upon clinical confirmation of a secondary malignancy, blood samples should be collected for cellular kinetic analyses by

qPCR and flow cytometry. Two tubes of blood are requested: 10 mL sample of peripheral blood mononuclear cells (PBMCs) in a sodium heparin collection tube and 6 mL of blood in an ethylenediaminetetraacetic acid (EDTA) tube. [redacted] Additional details for sample handling and shipping are outlined in the [Laboratory Manual].

10.2.4 Data Monitoring Committee

An independent DMC will assess safety data, and critical efficacy variables at regular intervals.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.5 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, and Novartis representatives. The SC will review safety and efficacy data, and ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the Novartis clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a Steering Committee charter.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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, allow modification and/or verification of the entered data by the investigator staff. Designated investigator staff can refer to CCGs (CRF Completion Guidelines) as a guidance document for data entry in CRF.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (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 subject 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.

11.2 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 (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the medical dictionary for regulatory activities (MedDRA) terminology.

Subject IDs and visit occurrences will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis delegated CRO representative will review the protocol and data capture requirements (ie, electronic source (eSource), direct data entry (DDE) or electronic case report form (eCRFs)) 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 subject 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/clinical research associate (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 subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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,

[redacted]

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 subjects will be disclosed.

12 Data analysis and statistical methods

Majority of infused subjects will have aggressive r/r B-cell NHL. The aggressive r/r B-cell NHL is defined as subjects with subtypes BL, DLBCL, PMBCL and GZL. Due to rarity of FL in pediatric population, it is anticipated that only a very limited number of subjects will be enrolled. The primary interest is to estimate the efficacy of tisagenlecleucel therapy in subjects with aggressive r/r B-cell NHL who have measurable disease at baseline (baseline assessment prior to infusion for patients on bridging therapy should be done after completion of bridging therapy). The primary efficacy analysis will be based on all evaluable subjects with aggressive r/r B-cell NHL. The efficacy from subjects with FL will be listed separately. The safety analysis will include all subjects with r/r B-cell NHL. The primary efficacy and safety analysis will be conducted when all evaluable subjects with aggressive r/r B-cell NHL have been infused and followed for at least 6 months from study day 1 or discontinued early as well as at least 50% of those subjects have a Follow-up of at least 9 months. Infused subjects with follicular lymphoma will be listed descriptively. A final Clinical Study Report (CSR) will be produced once all subjects complete the study.

Any data analysis carried out independently by any investigators should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The analysis sets to be used are defined as below. Subjects with aggressive r/r B-cell NHL in 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 pharmacokinetics analysis.

12.1.1 Screened Set

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

12.1.2 Enrolled Set

The enrolled set comprises all subjects who are enrolled in this study. Enrollment is defined as the point at which the subject meets all inclusion/exclusion criteria, and the subjects' leukapheresis material is received and accepted for manufacturing.

12.1.3 Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects who received an infusion of tisagenlecleucel.

[redacted]

12.1.4 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) includes all subjects with aggressive r/r B-cell NHL who received infusion of tisagenlecleucel and had measurable disease at baseline.

12.1.5 Safety Set

The Safety Set comprises all subjects who received an infusion of tisagenlecleucel. In this study the Safety Set contains the same subjects as the FAS.

12.1.6 Cellular kinetic analysis set

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

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

[redacted]

12.1.8 Other analysis sets

Not applicable.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data will be listed by subject and/or summarized descriptively by subjects with aggressive relapsed/refractory (r/r) B-cell NHL and follicular lymphoma separately for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class, preferred term, and subjects with aggressive r/r B-cell NHL and follicular lymphoma separately.

12.3 Treatments

The total cells infused (cells) and total tisagenlecleucel transduced viable T cells infused (cells) will be listed and summarized by subjects with aggressive r/r B-cell NHL and follicular lymphoma separately using descriptive statistics. Subjects will be grouped into the following categories:

- Below the prescribed dose range
- Within the prescribed range

[redacted]

- 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 subject and summarized by the Anatomical Therapeutic Chemical (ATC) term. Transfusion during the study will be listed. In addition, whether subjects have received anti-cytokine medications for the management of CRS will be summarized.

12.4 Analysis of the primary endpoint(s)

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

12.4.1 Definition of primary endpoint(s)

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

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

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

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

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

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

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

See Appendix 1 for details of disease response criteria.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

The ORR along with the 95% Exact Clopper-Pearson confidence intervals will be summarized in subjects with aggressive r/r B-cell NHL in the EAS. The results of FL subjects (a very rare and indolent subtype) will be reported separately in a descriptive manner.

12.4.3 Handling of missing values/censoring/discontinuations

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

12.4.4 Sensitivity and supportive analyses

The primary analysis will also be performed on the Enrolled Set, FAS and on subjects who received a dose no less than the target dose range using the same methodology.

12.4.4.1 Subgroup analysis

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

- Age: <18 years, ≥18 years
- Gender: male, female
- Race: White, Asian, Other
- Ethnicity: Hispanic or Latino, Other
- Disease subtypes including BL, DLBCL, PMBCL, GZL
- Prior response status: Primary refractory, relapse without SCT, relapse after SCT
- Use of prior rituximab: Yes or No
- Stage of disease at baseline: I/II, III/IV

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

12.5 Analysis of secondary endpoints

The secondary objectives in this study include evaluating duration of response (DOR), event free survival (EFS), relapse free survival (RFS), progression free survival (PFS), overall survival (OS) and safety. Due to rarity of incidence, it is expected that a very limited number of subjects with FL will be enrolled. DOR, EFS, RFS, PFS and OS will be analyzed only in subjects with aggressive r/r B-cell NHL. Kaplan-Meier (KM) analyses will be performed if adequate number of events are observed. DOR, EFS, RFS, PFS and OS for subjects with FL will be listed. Local investigator assessment will be used for secondary endpoints that involve disease response.

12.5.1 Efficacy and/or pharmacodynamic endpoint(s)

12.5.1.1 Duration of response (DOR)

Duration of response (DOR) applies only to subjects 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

[redacted]

PR) whichever occurs first, to the date of first documented relapse or death due to underlying cancer (at time of primary endpoint analysis).

In case a subject does not have progression or death due to underlying cancer prior to data cutoff, DOR will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be:

- Ongoing without event
- Lost to Follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling HSCT)
- Adequate assessments no longer available

Distribution of DOR will be estimated using the KM method in which death due to reason other than underlying cancer will be censored. DOR will be only summarized among subjects with aggressive r/r B-cell NHL.

As HSCT is an important treatment option in responding subjects, it is appropriate to consider the date of HSCT as censoring date, instead of censoring at the last tumor assessment date. If a subject received HSCT after a CR or PR, relapse or survival status after HSCT will be recorded on the corresponding Follow-up eCRFs. In such cases, the date of relapse or death (if due to underlying cancer) after HSCT will be used for the calculation of DOR as a sensitivity analysis.

In addition, the DOR may be separately summarized for subjects in aggressive r/r B-cell NHL with best overall response of CR and those with best overall response of PR.

12.5.1.2 Event free survival (EFS)

Event free survival (EFS) is the time from date of first tisagenlecleucel infusion to the earliest date of the following:

- Death from any cause
- Disease progression as determined by local investigator assessments
- New anticancer therapy for underlying cancer, excluding HSCT (at time of primary endpoint analysis)

In case a subject does not have any of the above events prior to data cutoff, EFS is censored at the last adequate response assessment date on or prior to the earliest censoring event (except for HSCT). The censoring reason could be:

- Ongoing without event
- Lost to Follow-up
- Withdrew consent
- HSCT (see below for handling of HSCT)
- Adequate assessments no longer available

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

[redacted]

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

EFS will be only analyzed among subjects with aggressive r/r B-cell NHL.

12.5.1.3 Relapse free survival (RFS)

Relapse free survival applies only to subjects 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, whichever occurs first) to the date of first documented relapse or death due to any cause (at time of primary endpoint analysis).

In case a subject does not have progression or death due to any cause prior to data cutoff, RFS will be censored at the date of the last adequate disease 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 HSCT)
- Adequate assessment no longer available

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

RFS will be assessed only in subjects with the best overall response of CR or PR. The distribution function of RFS will be estimated using the KM method. The median RFS along with 95% confidence intervals will be presented if appropriate. RFS will be only analyzed among subjects with aggressive r/r B-cell NHL.

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

In case a subject does not have progression or death prior to data 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)
- Adequate assessments no longer available

[redacted]

In the main analysis of PFS, subjects 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.

PFS will be estimated using the KM method and the median PFS as well as proportion of subjects without event at 3, 6, 9, and 12 months will be presented along with 95% confidence interval. PFS will be only analyzed among subjects with aggressive r/r B-cell NHL.

12.5.1.5 Overall survival (OS)

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

Subjects not known to have died at the data cut-off date are censored at their last contact date, which is defined as the latest date they were known to be alive. Subjects were followed for survival also in case of HSCT. OS will be summarized censoring for SCT as sensitivity analysis.

The distribution function of OS will be estimated using the KM method. The median OS along with 95% confidence intervals will be presented if appropriate. OS will be only analyzed among subjects with aggressive r/r B-cell NHL.

12.5.2 Safety endpoints

12.5.2.1 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 aggressive r/r B-cell NHL and follicular lymphoma separately and combined in Safety set.

The overall observation period for safety endpoint analysis will be divided into three mutually exclusive segments:

- **Pre-treatment period:** from day of subject'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 applies to subjects who received lymphodepleting chemotherapy): from the first day of lymphodepleting chemotherapy to the day before infusion of tisagenlecleucel, for subjects who received infusion, or to the earlier of date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy for subjects who didn't receive infusion of tisagenlecleucel.
- **Post-infusion period:** starting at day of tisagenlecleucel infusion until EOS.

12.5.2.2 Adverse events (AEs)

Reporting of adverse events will be based on the most current Medical Dictionary for Regulatory Activities (MedDRA) and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Adverse events that begin or worsen after informed consent should be recorded in the subject's source documents. New or worsening adverse events prior to starting study treatment (ie, lymphodepleting chemotherapy or the pre-infusion visit if the lymphodepleting chemotherapy

is not given) or are not required to be recorded in the CRF unless it is an AE meeting criteria or SAE meeting criteria. Once the subject begins 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 started or worsened during the post-infusion period, ie, the tisagenlecleucel treatment-emergent AEs. In addition, AEs that started or worsened during the lymphodepleting period will be summarized for all subjects who received lymphodepleting chemotherapy. All safety data (including those from the pre-treatment period) will be listed along with the period of the starting date of AE.

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, seriousness, severity (based on CTCAE grades), and relation to study treatment. A subject with multiple CTCAE grades for an AE will be summarized under the maximum CTCAE grade recorded for the event. The frequency of AEs of grade 3 or above will be summarized together.

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

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

12.5.2.4 Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities will be flagged.

12.5.2.5 Performance status and tanner staging

All performance status and tanner staging data will be listed.

12.5.2.6 Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) CTCAE version 5.0. 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:

[redacted]

- 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 common terminology criteria (CTC) grades and the classifications relative to the laboratory reference ranges.

[redacted]

12.5.2.7 Immunogenicity

The humoral immunogenicity assay measures the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. Data will be further fractionated to determine proportion of subjects who make transient versus sustained antibody responses. The cellular immunogenicity assay assesses the presence of T lymphocytes activated by the tisagenlecleucel protein. Data will be reported as summary statistics of pre and post-dose levels of activated T lymphocytes. [redacted] Further details will be provided in the statistical analysis plan (SAP).

12.5.2.8 Percentage of subjects who undergo HSCT after tisagenlecleucel therapy

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

- While in remission
- After relapse

12.5.2.9 Cytokine release syndrome

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

12.5.3 Pharmacokinetics

Tisagenlecleucel transgene and CAR transgene will be used interchangeably throughout the document. The tisagenlecleucel cells, as quantitated by flow cytometry, refers to the CAR positive T cells.

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

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

[redacted]

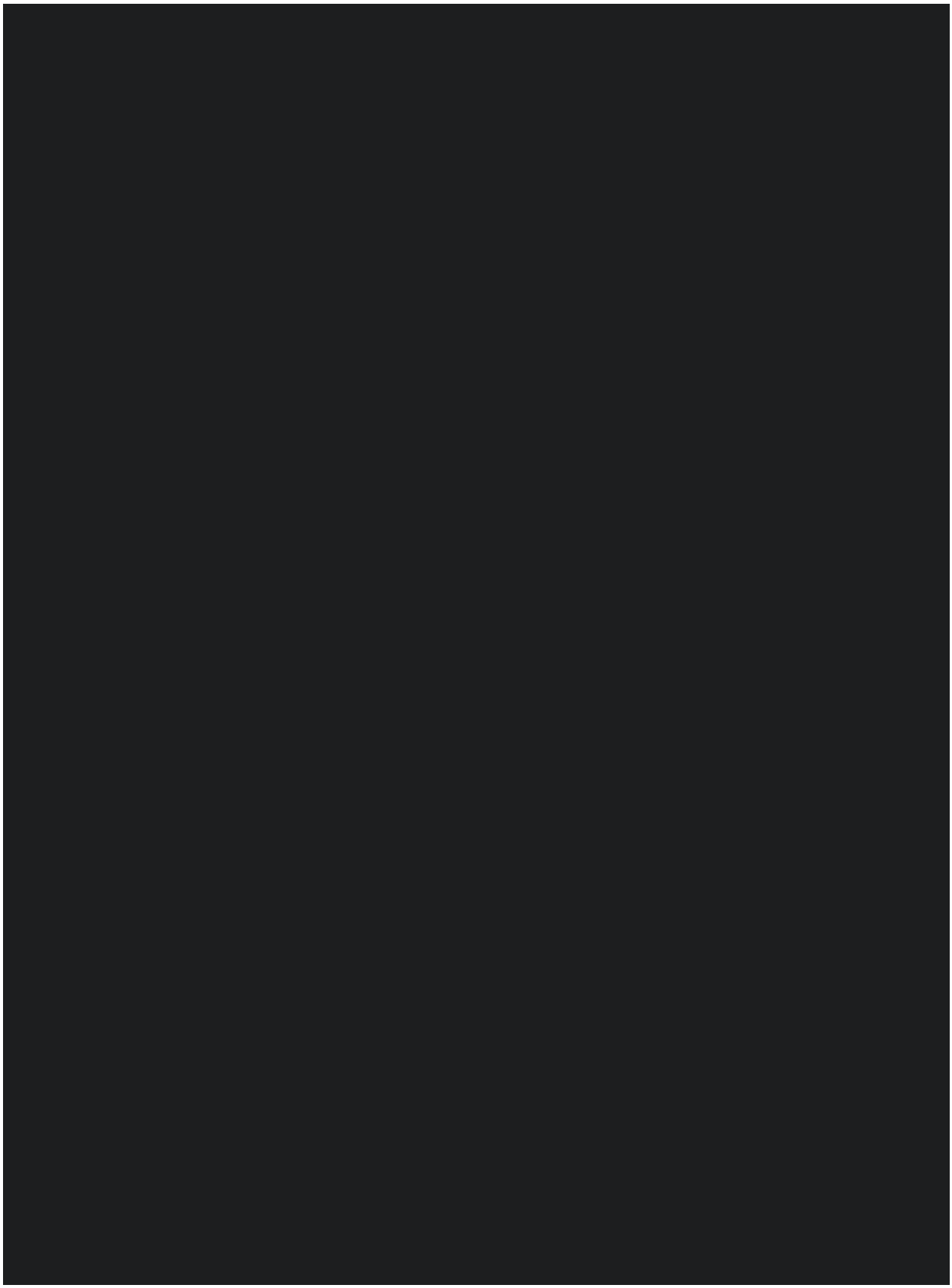
The cellular kinetic parameters listed in Table 12-1 along with other relevant cellular kinetic parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix® (Pharsight, Mountain View, CA) and reported by Month 3 (±14 days) response category.

Table 12-1 Non-compartmental pharmacokinetic 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
Clast	The last observed quantifiable concentration in peripheral blood (% or copies/µg)
Tlast	The time of last observed quantifiable concentration in peripheral blood (days)

[redacted]

[redacted]



12.7 Interim analyses

Not Applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

It is planned to enroll approximately 35 subjects with an aim to infuse at least 26 evaluable subjects with aggressive r/r B-cell NHL (BL, DLBCL, PMBCL and GZL) for the primary ORR analysis. The primary objective of the study is to estimate response rate and therefore the sample size is not based on power calculation. Among 26 subjects with aggressive r/r B-cell NHL, ORR will be descriptively summarized with the point estimate along with 95% exact CIs. With a sample size of 26 subjects, the 95% exact CI assuming various observed response rates are displayed in Table 12-2.

Table 12-2 95% exact confidence interval assuming various observed response rates

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

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

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed 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.

13.2 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, subject recruitment procedures (eg: advertisements) and any other written information to be provided to subjects. 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.

13.3 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 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 (eg: 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.

13.4 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 standard operating procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and health authorities, where required, it cannot be implemented.

[redacted]

14.1 Protocol Amendments

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 prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject 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.

[redacted]

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16 Appendices

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

16.1.1 Introduction

The purpose of this document is to provide working definitions and rules to evaluate efficacy in pediatric patients with non-Hodgkin lymphoma (NHL), in studies conducted by Novartis. This document is based on the consensus of a multidisciplinary international (North America, Europe, and Australia) collaboration of experts in pediatric oncology, hematopathology, radiology, and NHL biology held in 2009 and 2012 at the Third and Fourth International Symposia respectively, on Childhood, Adolescent and Young Adult NHL, the International pediatric non-Hodgkin lymphoma response criteria (Sandlund et al 2015) and the Lugano Classification (Barrington et al 2014, Cheson et al 2007, Cheson et al 2014).

16.1.2 Methodology and Definitions

16.1.2.1 Computed tomography (CT)/Magnetic resonance imaging (MRI)

For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline/pre-infusion and during Follow-up. Contrast-enhanced CT or MRI 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 ≤5 mm slice thickness with a contiguous reconstruction algorithm. 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 neck, abdomen and pelvis (MRI of the chest is not recommended due to respiratory artifacts). MRI is the preferred imaging modality for evaluating central nervous system (CNS) disease. CT scan is superior for assessing the lungs, and MRI is superior for assessing the marrow.

16.1.2.2 Fluorodeoxyglucose-Positron emission tomography (FDG-PET)

PET scans should cover the whole body from base of skull to mid-thigh. Examinations should be consistent across all time points when performed 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, duration of fasting, and glucose level should be collected for each time point. The PET images should be converted to standardized uptake value (SUV) maps to support comparison across time points and to standardize viewing conditions.

16.1.2.3 PET-CT

Hybrid PET-CT with diagnostic CT scanners may be used to acquire PET and CT images if the CT produced by the scanner is of diagnostic quality, and includes i.v. contrast. Non-diagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only CT scan for the time point.

[redacted]

If the diagnostic CT and PET are acquired on the same day, it is strongly recommended that the PET is performed prior to the CT with IV contrast as to not compromise PET results. Thus, one of the three following imaging methodologies is possible in a lymphoma study:

Table 16-1 Possible imaging methodologies in lymphoma study

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

16.1.2.4 PET-MRI

Hybrid PET-MRI whole body with contrast enhancement may be acquired instead of a PET-CT scan, in a manner similar to PET-CT. A PET-MRI with MRI coverage of the neck, chest, abdomen and pelvis plus a CT of the chest should be obtained (MRI of the chest is not recommended due to respiratory artifacts), Section 16.1.2.3.

16.1.2.5 Handling Changes in Imaging Technique

The same imaging modality should be used at baseline and all subsequent assessments to allow for consistency across assessments and to reduce the risk of false and unknown responses based on differences in imaging modalities.

If a change in the imaging modality has occurred during the study (eg: a switch from CT to MRI, a switch from i.v. contrast to non-contrast, or a switch from a diagnostic quality CT to an attenuation correction CT), the reviewer will determine whether this change in technique affects tumor evaluation. If, in the opinion of the reviewer, there are too many differences in the exams, resulting into non-evaluation of disease burden identified at baseline, the response will be unknown (UNK), unless there is clear evidence of progression.

Note: for time points that do not require PET imaging this rule does not apply (e.g. evaluation 1 includes a CT neck, chest, abdomen, pelvis vs evaluation 2 includes PET imaging and a CT neck, chest, abdomen, pelvis). The radiological response that does not include PET imaging should not be assessed as UNK due to the missing PET, Section 16.1.4.4.1 and Table 16-2.

16.1.3 Definitions

16.1.3.1 Disease stage

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

16.1.3.2 Screening

Measurable disease by radiological criteria within 8 weeks of screening visit must be established locally by investigator to meet eligibility and enrollment criteria for study. For patients with Burkitt leukemia, measurable disease by bone marrow assessment is sufficient if radiological criteria are not met.

[redacted]

16.1.3.3 Baseline/Pre-Infusion

Baseline examination should be as close as possible to the date of randomization/start of treatment, preferably within 2 weeks prior to date of randomization/start of treatment and after completion of any bridging therapy. Patients with no measurable disease at baseline will continue efficacy Follow-up as per the protocol visit evaluation schedule and maintenance of complete response (CR), or progressive disease (PD) will be assessed at post-infusion time points.

16.1.3.4 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)

16.1.3.5 Measurable Disease

All anatomic measurements should be taken in two perpendicular dimensions and recorded in metric notation. Throughout this document, a lesion will be called measurable if:

- It can be measured accurately in 2 perpendicular dimensions: longest diameter (LDi) (also known as transverse diameter), and short diameter (SDi), which is the longest short diameter perpendicular to LDi (also known as perpendicular diameter). The LDi and SDi must be measured on the same slice.
  - For patients ≥12 years of age:
    - For a nodal lesion, LDi must be >15 mm, regardless of SDi
    - For an extranodal lesion, both LDi and SDi must be >10 mm
  - For patients <12 years of age who do not meet the above criteria, measurable disease will be determined by the investigator, based on what threshold of measurements would be considered abnormal at baseline in this age group.

  Note: The baseline threshold established by the investigator must be documented in the source document and the CRF and should be applied to all subsequent assessments of measurable and non-measurable disease described in this document.

A lymph node not meeting the measurability criteria but with LDi >15 mm (eg: 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 neither a measurable nor a non-measurable nodal lesion for FDG-avid histologies.

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

Patients with Burkitt leukemia must have >25% bone marrow involvement by disease if radiological criteria are not met.

[redacted]

16.1.3.6 Bulky Disease

Bulky disease will not be classified as a separate entity and shall be captured by means of response criteria and sum of the product of the perpendicular diameters for multiple lesions (SPD).

16.1.3.7 Non-Measurable Disease

Non-measurable disease refers to all other lesions, including small lesions (eg: longest diameter <10 mm with CT/MRI or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions eg: blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.1.3.8 Index Lesions/Target Lesions. Index or target lesions are considered the same and will be referred to as index lesions in the document

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

16.1.3.9 Non-index/Non-target Lesions. Non-index or non-target lesions are considered the same and will be referred to as non-index lesions in the document

- All measurable disease not selected as index lesions but are consistent with lymphoma
- All non-measurable disease

16.1.3.10 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 non-measurable lesion attributable to lymphoma (eg: ascites, pleural effusion)

16.1.4 Efficacy assessments

16.1.4.1 Eligibility

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

[redacted]

16.1.4.2 Methods of disease assessment

16.1.4.2.1 PET Combined with Diagnostic CT Scan

The integration of PET into more frequently acquired CT evaluation may 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 Table 8-1 and Table 8-2. PET scans should be performed at pre-specified times during and/or after treatment. PET may also be acquired to confirm CT and PD results. Response assessments made after a change in imaging modality should be queried to confirm the change in the modality and the response assessment provided.

In order to calculate the sum of the product of the perpendicular diameters (SPD) of all index lesions, the appropriate dimensions of the lesions 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 (eg: 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 (ie, borders of the lesion are confounded by 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 a single lesion, report the overall diameters to one of the lesions and assign 0 mm × 0 mm to each of the other previously measured lesions. Subsequently, the product of the perpendicular diameters (PPD) of the confluent mass should be used to assess response. Disease progression is indicated by an increase of more than 25% in the PPD of the confluent mass compared with nadir of the sum of the product of perpendicular diameters (SPD) of the individual nodes.

If a lesion splits into several discrete lesions, the individual product of the perpendicular diameters (PPDs) of each discrete lesion should be summed together to represent the PPD of the entire 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).

16.1.4.2.2 Bone marrow assessment

Bone marrow evaluation by biopsy or aspirate (if adequate quality and volume), should be performed for all patients at screening, locally by investigator. All patients with lymphomatous bone marrow involvement at screening and as clinically indicated, should undergo additional bone marrow assessments, by biopsy or aspirate, 2 weeks prior to infusion (baseline) to reassess disease burden and post-infusion, to confirm any radiological response. Bone marrow biopsy/aspirate results will take precedence over bone marrow assessment reported by imaging for overall disease assessments. After confirmation of CR by bone marrow assessment (for patients with diagnosis other than Burkitt leukemia), further bone marrow assessments are not required and should be performed as clinically indicated by the investigator. Patients who have negative bone marrow involvement at screening are not required subsequent assessments unless clinically indicated.

[redacted]

Patients with Burkitt leukemia are required to have bone marrow assessments performed at day 28, month 3, month 6, month 9, and month 12 visits, and then as clinically indicated.

16.1.4.2.3 CSF Assessment

Cerebrospinal fluid (CSF) evaluated by lumbar puncture in all patients at screening. Patients with CSF involvement at screening should be excluded from study participation (Protocol Section 5). CSF assessments should be conducted at any time while on study as clinically indicated by the investigator.

16.1.4.2.4 Physical examination

Cutaneous lesions must be histologically confirmed for lymphomatous involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding CRF) and submit photograph(s) including a scale/ruler ((color photography using digital camera). Response assessment of cutaneous lesions will be performed and results will be recorded on the corresponding CRF at baseline and at the time of each radiological assessment.

16.1.4.3 Documentation of disease

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

16.1.4.3.1 FDG Update

FDG uptake in nodal and extranodal site that is suggestive of lymphoma will be assessed using five-point scale PET Five Point Scale (5PS).

16.1.4.3.2 Index lesions

A minimum of one measurable index lesion and 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 selected index 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 lesions should be selected on the basis of their size and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Index nodal lesions

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 different regions of the body including mediastinal and retroperitoneal areas of disease whenever these sites are involved.

[redacted]

Index extranodal lesions

Extranodal lesions in organ such as lung, liver and kidney may be included up to six index lesions to be assessed throughout the study if attributable to lymphoma. Lymphomatous involvement of non-FDG avid lesions, and cutaneous lesions should be assessed histologically. If such lesions are measurable and histological assessment is consistent with lymphoma, then they may be selected as index lesions.

16.1.4.3.3 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 extra nodal lesions

Measurable extranodal lesions not selected as index lesions and all non-measurable disease 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.

16.1.4.3.4 Spleen Involvement

The spleen will be assessed qualitatively for enlargement on the basis of CT and/or MRI scans, however no measurements will be recorded unless index lesions are noted. Assessment of spleen size should be performed before start of treatment and if present should be assessed at baseline. The spleen involvement should be reassessed on study as “Enlarged”, “Normalization (normal size for nodal lesions or absent for extra-nodal lesions)”, “Neither normalization nor unequivocal progression”, “Unequivocal progression” or “Not assessed”. Enlarged spleen, not attributable to lymphoma will not prevent a CR if rest of the disease burden has disappeared. Discrete intrasplenic lesions should be followed as index, non-index and new extranodal lesions, and splenic enlargement should be followed as non-index and new extranodal lesions.

16.1.4.3.5 Liver involvement

Given variability in physical habitus and the impact of numerous medical conditions, liver size by physical examination or CT scan is not considered a reliable measure of quantifying hepatic involvement by lymphoma, hence organomegaly alone is not sufficient to support lymphomatous involvement of the liver in this trial. Diffusely increased or focal uptake, with or without focal or disseminated nodules, supports liver involvement. Intrahepatic lesions should be followed as index or non-index lesions throughout the trial.

16.1.4.3.6 CSF Involvement

CSF involvement should be documented in the CRF as “Yes” or “No” at each lumbar puncture.

[redacted]

16.1.4.3.7 Bone marrow involvement

Lymphomatous involvement of bone marrow should be documented in the CRF as "Yes" or "No" at each bone marrow assessment by biopsy and/or aspiration.

16.1.4.3.8 PET 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 (Barrington et al 2014). The 5PS scores the most intense uptake in a site of disease (Table 16-2).

Table 16-2 Five Point Scale (5PS) to determine FDG uptake

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 of 3 will be considered negative

* 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 at least 2 times greater than the maximum SUV in the liver. The 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).

16.1.4.4 Response Evaluation

The efficacy variables in the statistical analysis are based on **overall disease response** (Table 16-4), which is a combined evaluation of response based on all components of radiological, bone marrow, CSF and clinical findings, and is determined at each post-baseline assessment. The radiological, bone marrow biopsy/aspirate, CSF, and additional clinical assessments are evaluated as defined in the International pediatric non-Hodgkin lymphoma response criteria [IPNHLRC] and the Lugano 2014 criteria (Table 16-3) and overall disease response is then determined by taking into account all the above criteria (Table 16-4).

16.1.4.4.1 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/MRI response** based on anatomical measurements of index/non-index/new lesions. The possible response outcomes are complete response (CR), partial response (PR), minor response (MR), no response (NR), progressive disease (PD) or unknown (UNK) as defined in Table 16-3.
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

[redacted]

(PMR), no metabolic response (NMR), progressive metabolic disease (PMD) and unknown (UNK), as defined in Table 16-3.

3. **Overall radiological response** combines CT/MRI response with PET response. The outcomes include CR, PR, MR, NR, PD and UNK. For time points when both CT and PET are available, if PET and CT responses are inconsistent for a given time point, PET response will take precedence. If at a particular time point, only a CT/MRI assessment is performed, the PET response obtained at a different time point (previous or subsequent to the current time point being assessed) may be taken into account to determine the overall radiological response.
   Note: Chest x-ray and ultrasound should not be used to measure tumor lesions.

When only CT/MRI imaging is available, only the CT/MRI response will be determined.

When CT/MRI and PET imaging is available all response assessments (CT/MRI response, PET response and the overall radiological response) will be possible, when PET imaging is not available only CT/MRI based response will be possible. The metabolic response designation will only be applied for the radiological response when PET imaging is available, the CT/MRI response and overall disease response will consist of the standard response conventions.

Example: *A CT response of PR at the same assessment as a PET response of CMR will constitute an overall radiological response of CR, and - a subsequent time point with CT only and CT response of CR. The overall radiological response of CR is possible when PET imaging is not available if there is no change in anatomical location or a prior PET scan showed a CR.*

[redacted]

Table 16-3 Definitions of response criteria

Overall Response Criteria		CT/MRI based response	PET-based response (Only when PET imaging is available)	Biopsy/ Aspirate/ other assessments	CNS disease on CSF when available	New Disease	Bone marrow (BM)
Complete Response (All of the following)	**CR**	CR (Disappearance of all index and non-index disease by CT/MRI) Spleen: Normalized[a]	†5PS of 1, 2, or 3 **without** residual mass on 5PS (CMR)	**Resected residual mass that is pathologically (morphologically) negative for disease**	Negative	None	Negative
	CRb	PR/SD/NN (Residual mass present on CT/MRI) Spleen: Normalized[a]	†5PS of 1, 2, or 3 **with residual mass** on 5PS (CMR)	**Residual mass has no morphologic evidence of disease from limited or core biopsy**	Negative	None	Negative
	CRu	PR/SD/NN (Residual mass present on CT/MRI) Spleen: Normalized[a]	†5PS of 1, 2, or 3 **with residual mass** on 5PS(CMR)	N/A	Negative	None	Negative
Partial Response (All of the following)		Index: ≥50% decrease from baseline in SPD of all index lesions (Morphologic detection of disease in a biopsy sample of the mass may be present) Non-Index: Non-PD Spleen: Non-PD	†5PS of 4 or 5 with reduced uptake compared to baseline with respect to SUV intensity or extent. This may apply to the specific hottest lesion and/or overall. It is expected that there will be residual mass(es) present (PMR)	N/A	Negative	None	Persistent morphologic detection of disease in the BM if it was present at baseline; however, there should be a >50% reduction in the percentage of lymphoma cells

[redacted]

Overall Response Criteria	CT/MRI based response	PET-based response (Only when PET imaging is available)	Biopsy/ Aspirate/ other assessments	CNS disease on CSF when available	New Disease	Bone marrow (BM)
Minor Response (All of the following)	Index: Decrease in SPD >25% but <50% on CT or MRI Non-Index: Non-PD Spleen: Non-PD	†5PS of or 4 or 5 with reduced lesion uptake compared with baseline with respect to SUV intensity or extent (PMR) **OR** †5PS of 4 or 5 with no significant change in FDG uptake from baseline (NMR)	N/A	Negative	None	Morphologic evidence of disease, if present at baseline; however, there should be 25% to 50% reduction in percentage of lymphoma cells
No Response (All of the following)	No criteria for CR, PR, MR or PD are met	†5PS of 4 or 5 with no significant change in FDG uptake from baseline (NMR)	N/A	Negative	None	Do not meet CR, PR, MR, or PD criteria
Progressive Disease (At least one of the following)	Index: >25% increase in SPD on CT or MRI Non-Index: Unequivocal progression Spleen: Unequivocal Progression	†5PS of 4 or 5 with increased uptake compared to the visually determined nadir with respect to SUV intensity or extent **OR** New FDG-avid foci consistent with lymphoma (PMD)	New/recurrent Disease, Positive for lymphoma	Development of new/recurrent morphologic evidence of disease in CSF	Present, attributable to lymphoma	New/recurrent morphologic evidence of disease in BM

Note: 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.

[a] Enlarged spleen, not attributable to lymphoma will not prevent a CR if rest of the disease burden has disappeared.

[redacted]

16.1.4.5 Overall Disease Response

Overall disease response is determined based on a consolidated approach, taking into account results from combined radiological assessment, bone marrow biopsy and/or aspirate, and other clinical findings that may be available, at each time point. Disease status at screening, baseline and efficacy during the study will be evaluated using the following:

- Radiological Imaging
- Bone marrow biopsy or aspirate
- CSF cytology
- Physical exam findings/cytology/biopsy evaluation

Of note, patients with lymphoma involvement detected in the baseline bone marrow biopsy/aspirate require a subsequent bone marrow biopsy/aspirate to be considered for overall disease response. Radiologic assessment of bone marrow involvement alone is not sufficient to consider a patient negative for bone marrow involvement in cases where there is lymphoma involvement of bone marrow at baseline. For example, if the combined radiological response assessment at Month 3 (±14 days) is CR/CMR (implying that PET-based bone marrow involvement at Month 3 (±14 days) was negative), the overall disease response would be a CR only when there is documentation of a bone marrow biopsy negative for lymphoma involvement. The same principle applies to CSF involvement. For example, if the combined radiological response is PR, but CSF results of a lumbar puncture at the same time point indicates new CSF involvement, the overall disease response would be PD.

Disease status at screening, baseline and overall disease response at each post-baseline assessment should be captured on the CRF, along with the date of assessment/response.

Clinical progression must be based on documented physical exam/clinical findings; confirmation by imaging and/or biopsy is recommended, but not mandatory.

[redacted]

Table 16-4 Overall Disease Response

Oncology Assessments of Complete Response (CR) Requires **ALL of the following**:			
CT/MRI-based or Combined CT/MRI and PET 5 Point Scale Assessment	**Bone Marrow biopsy/aspirate**	**Physical Exam Lesions; Cytology/Biopsy evaluation**	**CSF**
CR/CMR	• If bone marrow was **positive at baseline**, it has to be normal by morphology at post-infusion assessment. • If bone marrow was **negative at baseline**, bone marrow confirmation at post-infusion is not required. **NOTE:** Bone marrow evaluation by aspirate/biopsy must be performed within a ± 4 week window of imaging studies in order to be applied to the response assessment	None, or normalized/ disappeared if present previously; Any lesions of undetermined malignancy on CT/MRI should be benign by clinical results. Cytology/biopsy results should not demonstrate any evidence of disease. **NOTE:** Cytology/biopsy evaluation status must be performed within a ± 4 week window of imaging studies in order to be applied to the response assessment	Morphologically free of disease, when applicable
Oncology Assessments of Partial Response (PR) Requires that **one of the following assessment combination across each row is true**:			
CT/MRI-based or Combined CT/MRI and PET 5 Point Scale Assessment	**Bone Marrow biopsy/aspirate**	**Physical Exam Lesions; Cytology/Biopsy evaluation**	**CSF**
PR/PMR	CR/PR, when applicable	No new unequivocal lesions, and previously reported lesions not consistent with progression; Not consistent with progression	Morphologically free of disease, when applicable
CR/CMR	PR, when applicable	No new unequivocal lesions, and previously reported lesions not consistent with progression; Not consistent with progression	Morphologically free of disease, when applicable

Oncology Assessments of Minor Response (MR) Requires that **one of the following assessment combination across each row is true**:			
CT/MRI-based or Combined CT/MRI and PET 5 Point Scale Assessment	**Bone Marrow biopsy/aspirate**	**Physical Exam Lesions; Cytology/Biopsy evaluation**	**CSF**
MR and non-PD by PET when available	CR/PR/MR, when applicable	No new unequivocal lesions, and previously reported lesions not consistent with progression; Not consistent with progression	Morphologically free of disease, when applicable
CR/CMR/PR/PMR	MR, when applicable	No new unequivocal lesions, and previously reported lesions not consistent with progression; Not consistent with progression	Morphologically free of disease, when applicable
Oncology Assessments of No Response (NR) Requires that **one of the following assessment combination across each row is true**:			
CT/MRI-based or Combined CT/MRI and PET 5 Point Scale Assessment	**Bone Marrow biopsy/aspirate**	**Physical Exam Lesions; Cytology/Biopsy evaluation**	**CSF**
NR/NMR	CR/PR/MR, when applicable	No new unequivocal lesions, and previously reported lesions not consistent with progression; Not consistent with progression	Morphologically free of disease, when applicable
CR/CMR/PR/PMR/MR/NMR	NR, when applicable	No new unequivocal lesions, and previously reported lesions not consistent with progression; Not consistent with progression	Morphologically free of disease, when applicable

[redacted]

Oncology Assessment of Unknown (UNK) Requires that **one of the following assessment combination across each row is true**:			
CT/MRI-based or Combined CT/MRI and PET 5 Point Scale Assessment	**Bone Marrow biopsy/aspirate**	**Physical Exam Lesions; Cytology/Biopsy evaluation**	**CSF**
UNK/not done	CR/PR/MR/NR, when applicable	No new unequivocal lesions, and previously reported lesions not consistent with progression; Not consistent with progression	Morphologically free of disease, when applicable
CR/CMR/PR/PMR/MR/NR/NMR	UNK/not done post-infusion, when morphological evidence of disease at baseline AND not consistent with progression	No new unequivocal lesions, and previously reported lesions not consistent with progression; Not consistent with progression	Morphologically free of disease, when applicable
CR/CMR/PR/PMR/MR/NR/NMR	CR/PR/MR/NR, when applicable	UNK/not done post-infusion, when evidence of disease at baseline AND not consistent with progression	Morphologically free of disease, when applicable
Oncology Assessments of Progressive Disease (PD) Requires **at least ONE of the following**:			
CT/MRI-based or Combined CT/MRI and PET 5 Point Scale Assessment	**Bone Marrow biopsy/aspirate**	**Physical Exam Lesions; Cytology/Biopsy evaluation**	**CSF**
PD/PMD	New or recurrent involvement	New unequivocal lesion or previously reported lesions consistent with progression	New involvement

16.1.4.6 Efficacy analysis definitions

16.1.4.6.1 Best overall disease response

The best overall response (BOR) is the best overall disease response recorded from date of randomization/start of treatment until progressive disease or start of new anticancer therapy, whichever comes first.

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).

[redacted]

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

A best overall response of NR will be declared when at least one overall disease response of NR is available at least 6 weeks after start of treatment (and the patient does not qualify for CR, PR or MR). If a different minimum follow-up period for NR is more appropriate (eg: 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 start of treatment and the second scheduled post-baseline assessment (and the patient does not qualify for CR, PR, MR or NR).

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 start of treatment. If PD is observed after this maximum Follow-up period, and the patient does not qualify for CR, PR, MR or NR, 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.

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

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.

16.1.4.6.2 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 in Section 16.1.4.6.3.

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, survival will be censored at the date of last contact.

[redacted]

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, progression-free survival is censored at the date of the last adequate assessment as defined in Section 16.1.4.6.3.

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 or death due to lymphoma. If a patient has not had an event, time to progression is censored at the date of the last adequate assessment.

Duration of response

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 the first documented overall disease response 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 whose best overall disease response was 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 (ie, first patient first visit (FPFV) to last patient last visit (LPLV) used for the analysis) for patients who had a PFS event (ie, 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.

[redacted]

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 16.1.4.6.3.

Relapse free survival

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

16.1.4.6.3 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 (eg: PET-CT, CT, or MRI), bone marrow biopsy, CSF and additional biopsy assessment if overall disease response at that assessment is CR/PR/MR/NR/UNK
- the earliest date of all measurements including radiological assessment (eg: PET-CT, CT, or MRI), bone marrow biopsy, CSF and additional biopsy assessments if overall disease response at that assessment is PD

Start dates

For all “time to event” variables other than the duration of response and relapse free survival variables, the date of randomization/start of treatment will be used as the start date. For the calculation of duration of response and relapse free survival 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 and relapse free survival.

End dates

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.

[redacted]

- 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 16.1.5.2)
- 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, MR or NR 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).

16.1.4.6.4 Censoring and sensitivity analyses

Censoring reasons

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 16-5) will be calculated for each time to event variable based on the information reported.

[redacted]

Table 16-5 Censoring reasons

Time to event variables	Possible censoring reasons
OS	• Alive • Lost to Follow-up
PFS, EFS, TTP, RFS and DOR	• Ongoing without event • Lost to Follow-up • Withdrew consent • Death due to reason other than underlying cancer (only used for TTP and DOR) • New anti-cancer therapy added (except for EFS optional) • Event documented after two or more missing response assessments • 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 16.1.4.6.3. 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 16-6), as well as addressing the issues of missing response assessments during the study. The protocol Section 12 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 16.1.4.6, and using the draft FDA guideline on endpoints (FDA Guideline Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics-May 2007) as a reference, the following analyses can be considered:

Table 16-6 Options for event dates used in PFS, EFS, TTP, DOR, RFS

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
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 16.1.4.6.3.

[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, ie,

- (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.

[redacted]

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 eg: 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), ie, 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, example:

- By assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-6 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 report and analysis plan (RAP) documentation.

16.1.5 Data handling and programming conventions

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

16.1.5.1 Calculation of 'time to event' variables

Time to event = end date – start date + 1 (in days)

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

16.1.5.2 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 (eg: vital signs assessment, performance status assessment, efficacy assessment, laboratory, PK.)
- 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

[redacted]

16.1.5.2.1 Date of new anti-cancer therapy

The date of new anti-cancer therapy is the date of the 1st new antineoplastic therapy (including medicine, radiotherapy and surgery reported in the further antineoplastic therapy pages or from other sources (eg: HSCT page).

16.1.5.2.2 Incomplete assessment dates

All investigation dates (eg: 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 16.1.4.6.3). If all measurement dates have no day recorded, the 1st of the month is used.

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

16.1.5.2.3 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.

16.1.6 References (available upon request)

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; 32:3048-58.

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; 32:3059-67.

Cheson BD, Pfistner B, Juweid ME, et al (2007) Revised response criteria for malignant lymphoma. J Clin Oncol; 25:579-86.

FDA Guideline (2007) Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Sandlund JT, Guillerman RP, Perkins SL, et al (2015) International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncology; 33(18):2106-11.

16.1.7 Additional Information

16.1.7.1 Adaptation for use in maintenance/adjuvant settings

For study populations without measurable disease at baseline (eg: 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).

[redacted]

16.1.7.2 Relapsed Disease (RD)

Any of the following meets the definition of RD:

- Any new nodal lesion >15 mm in any axis (ie, 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
- ≥25% 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 (ie, complete disappearance of extranodal mass or 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

16.1.7.3 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, disease-free survival is censored at the date of the last adequate assessment. Similar censoring rules and reasons as the ones used for PFS can be applied.

[redacted]

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

Hepatitis B

1. Test for Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb) and Hepatitis B core antibody (HBcAb).
2. If all of these three tests are negative, the patient is eligible.
3. If HBsAb only is positive:
   a. The patient is eligible in the absence of signs of hepatitis (e.g. increase of AST/ALT).
   b. Test for HBV DNA in presences of signs of hepatitis (e.g. increase of AST/ALT).
4. If HBsAg is positive, the patient is **NOT** eligible.
5. If HBsAg is negative but either HBcAb or both HBcAB and HBsAb are positive, test for HBV DNA.
   a. If HBV DNA is positive, the patient is **NOT** eligible.
   b. If HBV DNA is negative, the patient is eligible.

Hepatitis C

1. Test for Hepatitis C virus antibody (HCV Ab).
2. If HBV Ab is negative, the patient is eligible.
3. If HCV Ab is positive, test for HCV RNA.
   a. If HCV RNA is negative, the patient is eligible.
   b. If HCV RNA is positive, the patient is **NOT** eligible.

Patients with a history of Hepatitis B or C should be managed according to the current guidance from the American Society of Clinical Oncology (Hwang et al 2015) and HCV Guidance from the American Association for the Study of Liver Disease-Infectious Diseases Society of America (2014-2018).

[redacted]

16.3 Appendix 3: Tisagenlecleucel modified data reporting

This guidance is used to determine whether or not an AE (non-serious, serious), 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 10.1.2, and then use the applicable row of this guidance to determine whether or not that event is to be recorded in the CRF.

[redacted]

Table 16-7 Adverse event reporting

	Signed ICF through start of lymphodepleting chemotherapy or pre-infusion visit	**Start of lymphodepleting chemotherapy or pre-infusion visit through Month 12 post tisagenlecleucel infusion**	**> Month 12 visit through End Of Study**
AEs (non-serious and serious)	All infections All laboratory abnormalities deemed clinically significant by the investigator All clinical AEs grade ≥3 All SAEs and deaths All AEs related to a study procedure All AEs leading to study discontinuation	All AEs(i.e., non-serious AEs and SAEs) including laboratory abnormalities deemed clinically significant by the investigator irrespective of causality	Any non-serious AEs ≥ Grade 3 and any SAEs irrespective of Grade with at least a possible causal relationship to tisagenlecleucel The following AEs (i.e., non-serious AE and SAEs, if not otherwise specified) should be reported to Novartis regardless of causality: AEs with fatal outcome Events related to a study procedure Serious neurologic disorder Serious or opportunistic infections, that fulfill any of the following criteria: • Require anti-infective treatment • Lead to significant disability or hospitalization • Need for surgical or other intervention Hepatitis B reactivation Progressive multifocal leucoencephalopathy (PML) Prolonged depletion of normal B cells/ Agammaglobulinemia New occurrence or exacerbation of an autoimmune disorder Hematological disorders (incl. aplastic anemia and bone marrow failure) Positive RCL test result New secondary T-cell or non T-cell malignancy other than the primary underlying malignancy Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene

Table 16-8 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 through EOS)
	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		All	Modified: Related to an AE (non-serious and serious) defined as reportable for this period Antineoplastic 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

	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 through EOS)
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**	**Inpatient/ICU OR Outpatient**
	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:** Record all antibiotics starting from day of infusion, even if given prophylactically			

[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 through EOS)
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**	**Inpatient/ICU OR Outpatient**
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** clinically relevant results (scheduled or unscheduled) for all AEs defined as reportable in Table 16-7 Record all other laboratory values if they are ≥ Grade 3 (not part of LTFU Study) 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]

16.4 Appendix 4: Liver event and laboratory trigger definitions and Follow-up requirements

Table 16-9 Liver Event and Laboratory Trigger Definitions

	Definition/threshold
Liver laboratory triggers	3 x ULN ALT/AST ≤5 x ULN 1.5 x ULN <TBIL ≤2 x ULN
Liver events	ALT or AST >5 × ULN
	ALP >2 × ULN (in the absence of known bone pathology)
	TBIL >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 TBIL >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
TBIL: total bilirubin; ULN: upper limit of normal

Table 16-10 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 (eg: conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBIL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
ALT or AST		
>8 × ULN	Discontinue the study treatment immediately (*if applicable*) Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (eg: conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBIL, 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 (eg: conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBIL, 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 drug (*if applicable*) Establish causality Record the AE and contributing factors (eg: conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBIL, 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 (eg: conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBIL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
>3 to ≤5 × ULN (subject is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
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 (eg: conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

[redacted]

Criteria	Actions required	Follow-up monitoring
TBIL (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 (eg: conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBIL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (eg: reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
>1.5 to ≤2 × ULN (subject is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study treatment immediately (*if applicable*) Hospitalize the subject Establish causality Record the AE and contributing factors (eg: conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBIL, 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 (eg: conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a] Elevated ALT/AST >3 × ULN and TBIL >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.

* 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

TBIL: total bilirubin; ULN: upper limit of normal

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]

16.5 Appendix 5: Specific renal alert criteria and actions and event Follow-up

Table 16-11 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 24h-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider subject hospitalization and specialized treatment
New onset dipstick proteinuria ≥3+ OR (Spot) urinary protein-creatinine ratio (PCR) ≥1g/g (or ≥100 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 sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] Corresponds to Kidney Disease, Improving Global Outcomes (KDIGO) criteria for Acute Kidney Injury

Table 16-12 Follow-up renal events

Assess, document and record in the appropriate CRF • Urine dipstick and sediment microscopy evidence of Drug Induced Nephrotoxicity (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 subject 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

16.6 Appendix 6: Graft versus host disease (GVHD)

Chronic GVHD is an immune-mediated disorder that may occur following allogeneic SCT. Manifestations include scleroderma, dry eyes, dry mouth, lichenoid oral changes, bronchiolitis obliterans, vanishing bile ducts, or weight loss. It is to be diagnosed specifically rather than diagnosed when acute GVHD-like syndromes develop late (beyond day +100) after any transplant or donor leukocyte infusion.

As part of the exclusion criteria for this protocol Section 5 regarding GVHD, the grading & staging assessment of acute GVHD will follow the criteria described below in Table 16-13, and the definition of chronic GVHD will follow the criteria described in Table 16-14.

Table 16-13 Staging and grading of acute Graft-Versus-Host Disease (adapted from Harris et al, 2016)

Extent of organ involvement			
	Skin	**Liver**	**Gut**
Stage			
1	Rash on <25% of skin[a]	Total bilirubin 2-3 mg/dL[b]	Diarrhea >500 mL/day[c] or persistent nausea[d]
2	Rash on 25-50% of skin	Total bilirubin 3-6 mg/dL	Diarrhea >1,000 mL/day
3	Rash >50% of skin	Total bilirubin 6-15 mg/dL	Diarrhea >1,500 mL/day
4	Generalized erythroderma with bullous formation	Total bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III		Stage 2-3 or	Stage 2-4
IV[f]	Stage 4 or	Stage 4	

[a] Use “rule of nines” or burn chart to determine extent of rash.

[b] Range given as total bilirubin. Downgrade by 1 stage if an additional cause of elevated bilirubin has been documented.

[c] Volume of diarrhea applies to adults. For pediatric subjects, the volume of diarrhea should be based on body surface area. Gut staging for pediatric subjects was not discussed at the Consensus Conference. Downgrade by 1 stage if an additional cause of diarrhea has been documented.

[d] Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.

[e] Criteria for grading given as a minimum degree of organ involvement required to confer that grade.

[f] Grade IV may also include lesser organ involvement but with extreme decrease in performance status.

Table 16-14 Definition of chronic Graft-Versus-Host-Disease

Definite and Possible Manifestations of Chronic GVHD		
Organ System	**Definite Manifestations of Chronic GVHD**	**Possible Manifestations of Chronic GVHD**
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia	Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis	Xerostomia, keratoconjunctivitis sicca
Gastrointestinal (GI) tract	Esophageal strictures, steatorrhea	Anorexia, malabsorption, weight loss, diarrhea, abdominal pain
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubinemia
Genitourinary (GU)	Vaginal stricture, lichen planus	Non-infectious vaginitis, vaginal atrophy
Musculo-skeletal/Serosa	Non-specific arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization	Arthralgia
Hematologic	None	Thrombocytopenia, eosinophilia, autoimmune cytopenias
Lung	Bronchiolitis obliterans	Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis
At any time point post-transplant, if there are ANY definite symptoms (column 2) then the symptoms should be identified as chronic GVHD.		
At any time point post-transplant, if there are any possible symptoms (column 3) but no definite symptoms, then it is at the physicians' discretion to identify as either acute or chronic GVHD.		
Acute and chronic GVHD cannot be present at the same time. Thus if #1 is fulfilled, then all manifestations of GVHD should be identified as chronic GVHD.		

Limited Chronic GVHD

- Localized skin involvement and/or liver dysfunction OR
- Involvement of only one target organ

Extensive Chronic GVHD

- Generalized skin involvement ≥50% of body surface area OR
- Localized skin involvement and/or liver dysfunction plus at least one of the following:
- Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis
- Eye involvement (Schirmer's test with <5 mm wetting)
- Involvement of minor salivary glands or oral mucosa on lip biopsy
- Involvement of any other target organs OR
- Involvement of at least two target organs

[redacted]