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Novartis Research and Development

Tisagenlecleucel

Clinical Trial Protocol CCTL019BUS03 / NCT04225676

A phase II, open label, multi-center trial to determine the efficacy and safety of tisagenlecleucel re-infusion in Pediatric and Adolescent Young Adult (AYA) patients with acute lymphoblastic leukemia experiencing loss of B cell aplasia

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALB	Albumin
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/SGPT
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/SGOT
ATG	Anti-thymocyte globulin
ATC	Anatomical Therapeutic Chemical
AYA	Adolescent Young Adult
B-ALL	B cell lineage acute lymphoblastic leukemia
BM	Bone Marrow
BMT	Bone Marrow Transplantation
BUN	Blood Urea Nitrogen
CAR	Chimeric Antigen Receptor
CBC	Complete Blood Count
CCGs	CRF Completion Guidelines
CD	Cluster of Differentiation
CD137	4-1BB costimulatory molecule
CFR	Code of Federal Regulations
CI	Confidence Interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CIF	Cumulative Incidence Function
CKAS	Celluar Kinetic Analysis Set
CLL	Chronic Lymphocytic Leukemia
Cmax	Maximum concentration
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CRF/eCRF	Case Report/Record Form; the terms CRF/eCRF can be applied to either EDC or Paper
CR	Complete remission
CRES	CART-cell-related-encephalopathy
Cri	Complete remission with incomplete blood count recovery
CRO	Contract Research Organization
CRP	C-Reactive Protein
CRS	Cytokine Release Syndrome
CSF	Cerebral Spinal Fluid
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography

[redacted]

CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte
CTL019 cells	CD 19 redirected autologous T cells (also called CART19 cells)
DOR	Duration of Response
DLBCL	Diffuse Large B Cell Lymphoma
DMC	Data Monitoring Committee
DMSO	Dimethylsulfoxyde
DNA	Deoxyribonucleic Acid
DRESS	Drug Reaction with eosinophilia and systemic syndromes
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic Data Capture
EFS	Event Free Survival
EMA	European Medicines Agency
ENS	Enrolled Set
EOS	End of Study
EOT	End of Treatment and Primary Follow-Up
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FL	Follicular Lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration
GGT	Gamma-glutamyltransferase.
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GVHD	Graft versus Host Disease
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICANS	Immune effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune effector Cell-associated Encephalopathy
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IL6R	Interleukin 6 receptor

[redacted]

IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD/IUS	Intrauterine Device/Intrauterine System
i.v.	Intravenous(ly)
KM	Kaplan Meier
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LISA	Lentivirus insertion site analysis
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
LP	Lumbar Puncture
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MAP	Master Analysis Plan
MAS	Macrophage Activation Syndrome
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Authorities
MHC	Major Histocompatibility Complex
MMC	Maternal microchimerism
MRD	Minimal Residual Disease
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
MUGA	Multiple Uptake Gated Acquisition
NCCN	National Comprehensive Cancer Network
NE	Norepinephrine Equivalent
NR	No Response
ORR	Overall Remission Rate
OS	Overall Survival
pALL	Pediatric Acute Lymphoblastic Leukemia
PB	Peripheral Blood
PE	Physical examination
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
pH	Hydrogen ion concentration; a measure of the acidity or basicity of an aqueous solution
PI	Principal Investigator
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PML	Progressive multifocal leukoencephalopathy

[redacted]

PPS	Per-Protocol Set
PR	Partial Remission
PT	Prothrombin Time
q-PCR	Quantitative Polymerase Chain Reaction
RCL	Replication Competent Lentivirus
RDC	Remote Data Capture
RMP	Risk Management Plan
r/r	Relapsed or refractory
SAE	Serious Adverse Event
SC	Steering Committee
scFv	Single chain Fv fragment of an antibody
SCT	Stem Cell Transplantation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Event
TNF	Tumor Necrosis Factor
TLS	Tumor Lysis Syndrome
TCR	T Cell Receptor
TCR-zeta	Signaling domain found in the intracellular region of the TCR zeta, gamma and epsilon chains
ULN	Upper Limit of Normal
VASST	Vasopressin and Septic Shock Trial
VH	Heavy Chain Variable Domain
VL	Light Chain Variable Domain
VSV-G	Vesicular Stomatitis Virus, Glycoprotein
WBC	White Blood Cell
WOCBP	Women of child bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline efficacy assessment	If multiple assessments are performed prior to re-infusion/randomization then the one closest temporally prior to re-infusion will serve as baseline assessment
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
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 study	The end of the study is defined as the last visit of the last subject
Final Enrollment	The point at which a patient meets all inclusion/exclusion criteria and the patient's additional dose of tisagenlecleucel is confirmed
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/treatment	The drug whose properties are being tested in the study
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial SRAP documentation
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. 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
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature 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
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 (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

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Amendment 1

Amendment 1 (23-Jun-2020)

Amendment rationale

At the time of this protocol amendment, (June 2020), the study is in start-up phase. 0 sites have been initiated and 0 patients have been screened.

The protocol is amended to clarify that tisagenlecleucel is not an investigational treatment. Participants in the trial will be prescribed commercial tisagenlecleucel by a physician and it will be administered in the course of medical practice. The trial is still considered interventional because of the required laboratory assessments and bone marrow assessments. This amendment is also intended to ease the participation burden on the patients by reducing the number of required patient visits, and implement clarifications to the original protocol. No changes were made as a result of a safety event.

This protocol amendment aims to make the following key changes:

1. Clarification that participants in this trial will receive commercial tisagenlecleucel, prescribed by the treating physician in the course of medical practice. This clarification is essential because the doses for re-infusion were previously manufactured for each individual patient as commercial product and the physician can request this additional dose at any time from Novartis.
2. Removed Pre-treatment and Day -1 visits from the schedule of assessments and references to them in Section 3. Day -1 assessments will now occur on Day 1, prior to patient's re-infusion.
3. Clarifies original protocol by requiring a bone marrow aspirate or biopsy at screening and at Day 28. Bone marrow aspirate or biopsy will be optional, performed if clinically indicated, at Month 3, Month 6 and Month 12.
4. Clarifies original protocol by adding HIV, Hepatitis B and C testing, and Serum immunoglobulin level testing to Table 8-1. These items were required by the original protocol but were not listed in the Assessment Schedule.
5. Modified Section 9.1.1 from discontinuation of study treatment to discontinuation of study. Tisagenlecleucel is not being provided as a study drug, and decisions to stop or continue treatment will occur outside of this trial. This section now describes criteria and procedures for discontinuing from the study.
6. Removed references to Independent Review Committee (IRC), because an IRC was not established for this trial.
7. Updated Section 8.5.3 to remove the biomarker assessments that are not being performed.
8. Corrected typo in the primary endpoint, to show that B cell aplasia is measured by circulating B lymphocytes ($\leq$ 50/μL), not ($\geq$50/μL).

[redacted]

9. Modified inclusion criteria 6(a) to remove requirement for 2 consecutive measurements, 1 week apart, when absolute B lymphocyte count is ≥ 50/µL.
10. Removed inclusion criteria 6(c) which required absolute B lymphocyte count of ≥ 200/µL.
11. Removed MRD negativity from secondary endpoint.

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 the protocol

The terms "study treatment" and "CTL019" were replaced throughout the document with the word tisagenlecleucel because the tisagenlecleucel is being prescribed by the physician in the course of medical practice and is not considered a study treatment.

Table 2-1: Endpoint for the primary objective has been updated to indicate B cell aplasia is measured by circulating B lymphocytes (< 50/µL)

Table 2-1: Endpoint for the secondary objective has been updated to capture patient with OOR and remove the MRD negativity requirement.

[redacted]

Section 3: Added that the tisagenlecleucel will be prescribed by a physician in the course of medical practice.

Section 3: Updated the definition of loss of B cell aplasia to require only one measurement for patients, (previously 2 were required for patients with absolute count ≥ 50/µL but less then 200/µL), which can be either absolute B lymphocyte count ≥ 50/µL or PB B lymphocyte ≥ 10% of the total lymphocytes.

Section 3: Removed references to Pre Treatment and updated Treatment and Follow-up from (Section 8.1.6) to (Section 8.1.5).

Section 3: Removed month 9 from the months where an efficacy assessment will occur.

Figure 3-1: Updated the study design figure

Section 4.2: Section updated to indicate the approved commercial dose range for tisagenlecleucel should be used.

Section 4.4: Added that there may be an interim analyses performed every six months annually for publication purposes.

[redacted]

Section 4.5: Deleted two paragraphs that were duplicate of two previous paragraphs in the section.

Section 5.1: Revised Inclusion Criteria #1 to indicate that all patients must have an additional dose of unexpired, commercial tisagenlecleucel available and prescribed by a physician in the course of medical practice.

Section 5.1: Revised Inclusion Criteria #6 to update the definition of loss of B cell aplasia to require only one measurement for patients, (previously 2 were required for patients with absolute count≥ 50/μL but less then 200/μL), which can be either absolute B lymphocyte count ≥ 50/μL or PB B lymphocyte ≥ 10% of the total lymphocytes.

Section 5.2: Updated Exclusion Criteria #7 to clarify that it is 72 hours prior to tisagenlecleucel infusion.

Section 6.1: Updated section to indicate that the tisagenlecleucel is not considered study treatment. The product will be released commercially to the treating physician when it is prescribed in the course of medical practice.

Table 6-1: Moved table from section 6.1.1 to section 6.1. Updated contents of table to reflect the use of commercial tisagenlecleucel which is prescribed by the treating physician in the course of medical practice.

Section 6.1.1: Updated section to indicate it is not applicable.

Section 6.1.8: Updated section to indicate the dose range is the approved dose range.

Section 6.2.2: Updated paragraph on Medication restrictions prior to leukapheresis to indicate Not Applicable.

Section 6.7: Removed sentence indicating each site will be supplied with study drug.

Section 6.7.1: Modified section title to Handling of Tisagenlecleucel

Section 6.7.1: Updated section to indicate the investigator will maintain a record of the commercial tisagenlecleucel administered to study participants in a drug accountability log.

Section 6.7.1: Updated the tisagenlecleucel disposal and destruction section to indicate that the package insert for commercial Kymriah should be referenced.

Table 8-1 and Section 8.1: Revised as follows:

- Updated Periods in row one to Screening, Treatment and End of Study.
- Revised Visit Names in row 2 to Screening, Enrollment, assessment period and End of Study.
- Removed pre-treatment visit and Day -1 visit and columns for pre-treatment visit assessments and D-1 assessments.
- Moved assessments previously required on D-1 to D1
- Added HIV & Hepatitis B and C testing, Serum immunoglobulin levels (IgG, IgA, IgM) to Screening visit.

[redacted]

- Added Bone Marrow Aspirate or Biopsy as a required procedure to Screening visit and D28 visit, and as an optional procedure to M3, M6 and M12 visits.
- Revised procedure CTL019 infusion to Re-infusion of prescribed, commercially available tisagenlecleucel

Section 8.1.5: Removed requirement to collect labs of special interest for all patients that experience a CRS.

Section 8.2.2: Added Prior antineoplastic therapies and MRD status to baseline characteristics

Section 8.3.1: Removed the data review by Independent Review Committee (IRC).

Section 8.4: Added CNS evaluation description to the Physical examination specifications.

Table 8-4: Added HIV & Hepatitis B & C testing and Serum immunoglobulin levels (IgG, IgA, IgM). Clarified that pregnancy test can be either serum or urine at D28, M3 and M6.

Table 8-6: Updated Day for the pre-dose sample to D1.

Section 8.5.3: Removed biomarker assessments that are not being performed in this trial.

Section 9.1.1: Revised Section to indicate requirements for discontinuing from study

Section 9.2: Clarified the definition of end of study.

Section 10.1.7: Updated section title to Reporting of Tisagenlecleucel errors including misuse/abuse. Added statement indicating that this section will remain applicable.

Section 11.2: Removed sentence referring to emergency code breaks as not applicable to this trial.

Section 12: Updated to indicate:

- The primary analysis of the study (primary, secondary [redacted] objectives) will occur after all patients complete the Month 12 visit or prematurely discontinue from the study.
- Interim analyses may be performed every six months for publication purpose.

Section 12.1.5: Clarified text defining the Per-Protocol Set.

Section 12.3: Clarified that the safety set will be used for the analyses described in this section.

Section 12.4.1: Updated primary endpoint to align with section 2.

Section 12.4.2: Updated primary efficacy analysis methods.

Section 12.4.3: Added statement that patients who proceed to HSCT while in remission after reinfusion will be censored at the time of HSCT.

Section 12.4.3: Added Statement that the volume of data generated due to the COVID-19 pandemic may also be assessed and sensitivity analyses will be performed, if deemed appropriate.

Section 12.4.4: Added statement indicating the impact of COVID-19 will be explored and as appropriate, a sensitivity analysis of the primary endpoint may be performed to assess the impact to the study.

[redacted]

Section 12.4.4.1: Clarified the fifth bullet by adding Patients with a loss of B cell aplasia.

Section 12.5: Clarifications to the wording to align with Section 2.

Section 12.5.1: Removed MRD negativity to align with Section 2.

Section 12.5.3: Created section for overall survival.

Section 12.5.4.2: Added definition of treatment emergent adverse events and clarified how AEs will be summarized.

Section 12.5.4.3: Removed urinary laboratory tests from the summaries that will be generated.

Section 12.5.4.5: Updated section to remove statement indicating malignant and normal B cell populations will be listed and summarized by patient and time point and removed the reference to section 10.6.1.

Section 12.5.5: Added clarification regarding the Pharmacokinetic Analysis Set and removed statement that the CKAS set will be used for the analysis of [redacted] biomarkers.

Section 12.5.6: Updated Section to Not Applicable and deleted duplicate text that already appears in Section 12.5.4.5.

Section 12.6: Corrected hyperlink and Section reference.

Section 12.7: Removed duplicate text.

References: Added missing citations.

Changes to the remainder of the document include grammatical corrects/clarifications of minor inconsistencies.

Where appropriate, the words study treatment and CTL019 have been replaced by Tisagenlecleucel throughout the document.

[redacted]

Protocol summary

Protocol number	CTL019BUS03
Full Title	A phase II, open label, multi-center trial to determine the efficacy and safety of tisagenlecleucel re-infusion in Pediatric and Adolescent Young Adult (AYA) patients with acute lymphoblastic leukemia experiencing loss of B cell aplasia
Brief title	Study of efficacy and safety of reinfusion of tisagenlecleucel in pediatric and young adult patients with Acute Lymphoblastic Leukemia
Sponsor and Clinical Phase	Novartis Phase II Multi-center
Investigation type	Biological
Study type	Interventional: Any research study that prospectively assigns human participants to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc. [WHO Definition]
Purpose and rationale	Reinfusion of one or more additional doses of tisagenlecleucel can restore B-cell aplasia in some patients with early evidence of poor or short persistence of CD19-directed CAR-T cells and improve durable remission rates. (Maude 2016) Frequently, tisagenlecleucel manufacturing will yield more than one dose. If a patient who was previously treated with tisagenlecleucel presents with evidence of B-cell recovery within 12 months following first infusion and has an additional cryopreserved tisagenlecleucel dose, reinfusion of one dose can be performed with the aim to restore B-cell aplasia and potentially prolong remission and leukemia control
Primary Objective(s)	Evaluate the incidence of B cell aplasia after re-infusion of tisagenlecleucel
Secondary Objectives	Evaluate the efficacy of reinfusion of tisagenlecleucel for loss of B cell aplasia as measured by overall remission rate (ORR) 12 months after tisagenlecleucel reinfusion, which includes CR and CR with incomplete blood count recovery (CRi) as determined by investigator assessment for pALL patients Evaluate event free survival (EFS) Evaluate Overall survival (OS) Evaluate the safety of reinfusion of tisagenlecleucel reinfusion therapy.
Study design	This is a multi-center Phase II study investigating the efficacy and safety of reinfusion of tisagenlecleucel in pediatric and young adult patients with ALL who were previously treated with tisagenlecleucel and experience B cell recovery. The study will be comprised of 54 patients with 49 evaluable pediatric and young adult patients up to and including 25 years of age who have been previously infused with commercial tisagenlecleucel once and have an additional dose of commercial tisagenlecleucel available and prescribed in the course of medical practice.
Population	Patients up to and including 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) who have been treated with commercial

[redacted]

	tisagenlecleucel once and have an additional dose available and prescribed to them in the course of medical practice.
Key Inclusion criteria	• Must have an additional unexpired dose of commercial tisagenlecleucel available which is prescribed by a physician in the course of medical practice • Patients who were previously treated with commercial tisagenlecleucel and present with evidence of B-cell recovery as defined by: – Peripheral blood (PB) absolute B lymphocyte count ≥ 50/μL, **OR** – PB B lymphocyte ≥ 10% of the total lymphocytes
Key Exclusion criteria	• Prior gene therapy other than tisagenlecleucel • Prior adoptive T cell therapy other than tisagenlecleucel • Active CNS involvement by malignancy • Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening • HIV positive test within 8 weeks of screening. False positivity should be excluded by antigen detection tests or nucleic acid tests that have been shown not to cross react with tisagenlecleucel vector.
Study treatment	Not applicable. A second dose (for re-infusion) of commercial tisagenlecleucel is not considered a study treatment because it is released commercially when prescribed by the treating physician in the course of medical practice.
Efficacy assessments	• B and T-cells by Flow Cytometry • CTL019 Pharmacokinetics by qPCR
Pharmacokinetic assessments	• CTL019 Pharmacokinetics by qPCR
Key safety assessments	All patients treated with tisagenlecleucel will be monitored for specific toxicities for 15 years following reinfusion, irrespective of their response to tisagenlecleucel
Data analysis	This study is an exploratory study to evaluate the incidence of B cell aplasia after reinfusion of tisagenlecleucel. Sample size was based on an exact test for single proportion to test the null hypothesis H0: p<=0.10. Where p is the percent of patients who establish B-cell aplasia during 12 months. If the true rate p>= 0.25, then with an one sided alpha level of 2.5% and at least 80% power, a minimum of 49 evaluable patients will be required for the study. Considering drop-out rate of 10%, a total of approximately 54 patients will be enrolled into the study. Primary analysis will be performed using the Full Analysis Set. For primary analysis, the proportion of patients who establish B-cell aplasia during 12 months will be presented together with an exact 95% Clopper-Pearson confidence interval. The null hypothesis will be rejected if the lower limit of the 95% confidence interval is greater than 0.10, demonstrating improvement after reinfusion. All secondary [redacted] variables will be summarized descriptively. Categorical data will be presented in frequencies and percentages. For continuous data descriptive statistics (mean, standard deviation, median, 25th and 75th percentiles, min and max) will be provided. Kaplan Meier's estimates

[redacted]

	will also be reported for the time to event variables. Summarized safety data will also be presented.
Key words	Acute lymphoblastic leukemia, tisagenlecleucel, CTL019, reinfusion

[redacted]

1 Introduction

1.1 Background

1.1.1 Overview of disease, epidemiology and current treatment

Acute lymphoblastic leukemia (ALL) is a hematological malignancy characterized by the proliferation of immature lymphoid cells in the bone marrow, blood, and other organs (Jabbour et al 2005).

ALL is primarily a disease of children, adolescents, and young adults. ALL is the most common childhood cancer, accounting for about 80% of all leukemia cases in children and approximately 26% of cancer diagnoses among children from birth to 14 years of age (Ward et al 2014).

According to SEER projections for 2017, approximately 5,970 new cases of ALL (both adults and children) will be diagnosed in the US (httpsseer cancergov/statfacts/html/alylhtml). The most recent SEER analysis of prevalence estimated that there were 81,837 patients living with ALL in the US in 2014.

The median age at diagnosis is 15 years old, and 56% of new cases from 2010 to 2014 were diagnosed in patients younger than 20 years of age.

Among children, B-cell lineage ALL constitutes approximately 88% of leukemia cases. Pediatric B-cell ALL (pALL) has remained the primary cause of pediatric cancer mortality in the past 30 years, even though the mortality rate has been declining (httpsseer cancergov/statfacts/html/alylhtml).

Current treatment for B cell malignancies include combinations of chemotherapy, radiation therapy, bone marrow transplantation, or peripheral blood and cord blood stem cell transplantation (SCT). Initial chemotherapy is typically administered over a 2 to 3 year period. With current first line multi-agent treatment regimens, the long term remission among children with ALL is greater than 80%. Fifteen to 20% of patients who achieve an initial remission will experience disease relapse. Although this can occur at any time after diagnosis, the majority of relapses occur within 2 years of initial treatment (Nguyen et al 2008).

Most patients (>85%) with relapsed ALL will achieve a second remission (Borwitz et al 2015); however, the challenge remains to maintain remission. Most children who relapse once will relapse again, and will ultimately succumb to their disease. Leukemia is still the leading cause of death in pediatric oncology (Borwitz et al 2015). Although no standard definition exists, ALL is considered refractory if a complete remission (CR) is not attained within 1-2 cycles of chemotherapy from the initial or relapse diagnosis. Refractory ALL in adults or children has a dismal prognosis and these are not candidates for SCT. Thus relapsed or refractory (r/r) ALL patients, both adult and pediatric, have significant unmet medical need (Maude et al 2018).

1.1.2 Historical experience with viral gene therapies

Retroviral vectors are highly effective gene delivery vehicles for inserting the foreign genetic material into the host cell.

Lentiviral vectors, a major subset of retroviral vectors, demonstrate distinct integration patterns compared to other retroviral vectors, which have been the predominant vector to date for gene

[redacted]

transfer studies. The integration pattern of lentiviral vectors tends to be inside active transcription units as opposed to upstream in the locus control region where the insertion would have a greater chance of up-regulating gene expression. In addition, lentiviral vectors have no enhancer activity in their LTR regions and have lower levels of poly-A read-through, all factors, which may improve gene transfer safety (Zaiss et al 2002). Thus, lentiviral vectors appear a safer alternative to retroviral vectors, which is supported by animal models (Montini et al 2006). Lentiviral vector trials have demonstrated more polyclonal patterns of vector insertion (Cartier et al 2009, Biffi et al 2011), with the exception of the first patient reported from a thalassemia trial (Cavazzana-Calvo et al 2010). Importantly, despite a very high transduction efficiency achieved using lentiviral vectors, molecular clonality studies have not indicated any reasons for concern, to date, in published clinical trials (Schambach et al 2013).

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

1.1.3 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-based approach involves engineering T-cells with sequences that encode antibody-based antigen recognition moieties linked to signaling domains. Unlike T-cell receptors (TCR), chimeric antigen receptors (CARs) allow the T-cells to specifically target and destroy tumor cells in a Major Histocompatibility Complex (MHC) independent manner (Mellman et al 2011).

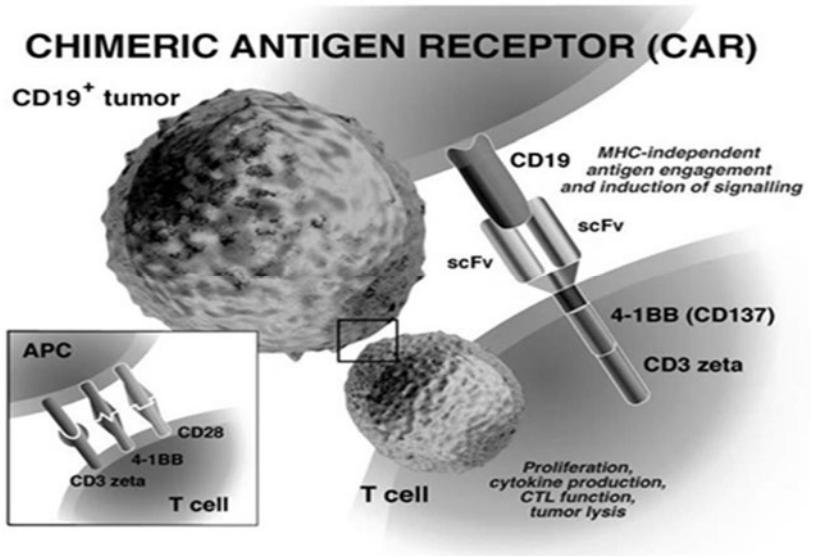
A promising target antigen for B-cell malignancies is CD19, a cell-surface protein whose expression is restricted to B-cells and their precursors (Sadelain et al 2003, Porter et al 2011), with no expression on hematopoietic stem cells or non-B cell tissues. It is a member of the immunoglobulin (Ig) superfamily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

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

Tisagenlecleucel (CART-19), a second generation CAR T cell therapy, is an adoptive cellular immunotherapy that uses the autologous peripheral blood T cells that have been genetically modified ex vivo to target CD19 on the surface of B-cells. As shown in Figure 1-1, the CAR approach uses genetically programmed T cells transfected with chimeric receptor genes to combine the effector functions of T cells with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner (Gross et al 1989, Pinthus et al 2003). These receptors have the ability to recognize intact membrane proteins independent of antigen processing. The tumor antigen binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the heavy chain variable domain (VH) and light chain variable domain (VL) joined by a peptide linker of about 15 residues in length (Mullaney et al 2001).

[redacted]

Figure 1-1 Tisagenlecleucel chimeric antigen receptor design



Recent clinical trials of tisagenlecleucel in r/r CLL, r/r ALL, and r/r B cell lymphomas (including follicular lymphoma (FL)) have shown promising and durable anti-tumor efficacy (Porter et al 2011, Grupp et al 2013, Maude et al 2014, Maude el al 2018, Schuster et al. 2017). Consequently, tisagenlecleucel appears to be a therapeutic alternative for patients with B cell malignancies (including FL) refractory to the current therapies. For further information refer to the [tisagenlecleucel Investigator's Brochure].

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

1.1.5 Clinical experience

Tisagenlecleucel is investigated in several B-cell malignancies including r/r ALL, r/r diffuse large B-cell lymphoma (DLBCL), r/r CLL, and FL. Available data showed encouraging anti-tumor efficacy with manageable toxicity (Grupp 2013, Porter 2011, Schuster 2017, Chong 2016, Maude 2018).

[redacted]

For more details please refer to the [tisagenlecleucel Investigator's Brochure].

1.1.5.1 Clinical efficacy

Tisagenlecleucel has been approved by the US FDA for the treatment of patients up to 25 years with B-cell precursor ALL that is refractory or in second or later relapse and for adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma [Kymriah Package Insert]. European Medicine Agency (EMA) has approved tisagenlecleucel for the treatment of pediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse, and of adult patients with r/r DLBCL after two or more lines of systemic therapy [EU SmPC 2018].

Efficacy in r/r pediatric and young adult ALL

The efficacy of tisagenlecleucel was demonstrated in a multi-center, global phase II study (B2202; ELIANA). In this trial, 75 children and young adults with r/r B cell ALL received an infusion of tisagenlecleucel. At enrollment, patients had a median age of 11 years, a median of 3 previous therapies (range, 1 to 8); 46 patients (61%) had undergone previous allogeneic HSCT. The overall remission rate (CR/CRi) was 81%; 45 patients (60%) had complete remission (CR), and 16 (21%) had complete remission with incomplete hematologic recovery (CRi). All patients who had a best overall response of CR or CRi were negative for minimal residual disease. The rate of relapse-free survival among patients with a response to treatment was 59% at 12 months. The majority of patients (89%) did not receive an allogeneic stem cell transplant after tisagenlecleucel. Updated data demonstrated a 24-month overall survival rate of 66%.(Maude et al 2018).

1.1.5.2 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 patients with refractory or relapsed B-cell precursor ALL, CRS was observed in 77% (21% Grade 3, 25% Grade 4). The median time to onset of CRS in this population was 3 days after infusion (range, 1 to 22). Neurologic events were reported in 40% of the patients (13% grade 3 and no grade 4). The most common other adverse events of any grade were infection (43%), pyrexia (40%), decreased appetite (39%), febrile neutropenia (35%), prolonged cytopenia (not resolved by day 28, 37%) and headache (36%). Tumor lysis syndrome was reported in 4% (Maude et al 2018).

1.2 Purpose

B-cell aplasia, which can be monitored by measuring CD19 positive B-cells by flow cytometry, is an expected on-target toxicity of successful CD19-directed CAR T-cell therapy. B-cell aplasia occurred in all the patients who had a response, and as long as CAR-modified T cells persist, B-cell aplasia continues. Therefore, B-cell aplasia provides what appears to be a highly accurate pharmacodynamic marker of tisagenlecleucel persistence (Maude 2014).

[redacted]

Tisagenlecleucel can produce potent, sustained responses in children and young adult patients with relapsed/refractory ALL. In the Eliana study, sustained remissions were associated with the persistence of tisagenlecleucel and B-cell aplasia (a surrogate marker for persistence), suggesting continued effector function. Some patients had tisagenlecleucel persistence of up to 2 years. The probability of tisagenlecleucel persistence at 6 months was 68% (95% CI: 50% to 92%) (Maude 2018). Yet a subset of patients do not respond or relapse due to poor CAR-T cell expansion and limited persistence. In Eliana 22% of patients had early B-cell recovery (within 6 months of tisagenlecleucel infusion). Early B cell recovery reflects poor tisagenlecleucel persistence and was associated with higher risk of relapse (Maude 2018).

Reinfusion of one or more additional doses of tisagenlecleucel can restore B-cell aplasia in some patients with early evidence of poor or short persistence and improve durable remission rates (Maude 2016) reported on retreatment or reinfusion with murine (CTL019 / tisagenlecleucel) or humanized (CTL119) CD19-directed CAR T cells. Of 55 patients in CR at 1 month after CTL019 infusion (55/59 CR), 3 patients received a repeat infusion of murine CTL019 for CD19+ relapse and 17 for poor persistence at 3 and/or 6 months after initial infusion (Maude 2016). Remission was achieved in 1/3 children treated for CD19+ relapse. Of 3 patients reinfused for CD19+ MRD, 1 progressed to CD19+ relapse, 1 became MRD- but had B cell recovery, and 1 had reduced MRD. Reinfusion induced B-cell aplasia for a second time in 1/7 children treated for B cell recovery, while 6/7 children reinfused for CD19+ hematogones demonstrated continued B-cell aplasia 6-21 months after repeat infusion. Of this group, 6 remained in remission 9-24 months after initial infusion, and 1 experienced a CD19- relapse. Eight children previously treated with CAR T-cells (CTL019, n = 5; other, n = 3) were treated on a phase 1 study of humanized CTL119 for B cell recovery (n = 3), CD19+ relapse (n = 4), or no response to prior CAR T-cells (n = 1). Cytokine release syndrome (CRS), seen in 4 patients, did not require vasopressor or respiratory support. Responses were seen in 4/8 patients with an ongoing CR of 7 months in 1 patient. 2/4 responding patients were previously resistant to reinfusion of murine CTL019.

Frequently, tisagenlecleucel manufacturing will yield more than one dose. If a patient who was previously treated with tisagenlecleucel presents with loss of B-cell aplasia, reinfusion may restore B-cell aplasia and potentially prolong remission and leukemia control.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• Evaluate the incidence of B cell aplasia after reinfusion of tisagenlecleucel	• Proportion of patients who establish B cell aplasia within 12 months of reinfusion, as measured by circulating B lymphocytes (< 50/µL) and presence of CTL019 cells by qPCR in the peripheral blood.
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**

Objective(s)	Endpoint(s)
• Evaluate the efficacy of reinfusion of tisagenlecleucel for loss of B cell aplasia as measured by overall remission rate (ORR) 12 months after tisagenlecleucel reinfusion, which includes CR and CR with incomplete blood count recovery (CRi) as determined by investigator assessment for pALL patients • Evaluate event free survival (EFS) • Evaluate Overall survival (OS) • Evaluate the safety of tisagenlecleucel reinfusion therapy	• Proportion of patients with ORR (= CR + CRi) per Investigator assessment in pALL patients during 12 months post-reinfusion • EFS, i.e. the time from date of tisagenlecleucel reinfusion to the earliest of relapse, treatment failure, or death • OS, i.e. the time from date of tisagenlecleucel re-infusion to the date of death due to any reason • Safety parameters including adverse events and laboratory abnormalities

[redacted]

3 Study design

A phase II, open label, multi-center trial to determine the efficacy and safety of tisagenlecleucel re-infusion in pediatric and AYA patients with acute lymphoblastic leukemia experiencing loss of B-cell aplasia. The patient population for this study will be comprised of 49 evaluable patients up to and including 25 years of age who have been previously infused with commercial tisagenlecleucel and have an additional dose of commercial tisagenlecleucel available and prescribed by a physician in the course of medical practice

Additionally these patients must have loss of B-cell aplasia defined as:

- Peripheral blood (PB) absolute B lymphocyte count ≥ 50/µL, OR
- PB B lymphocyte ≥ 10% of the total lymphocytes

Efficacy in this setting will be defined as establishing B cell aplasia.

The efficacy of the following sub populations will also be evaluated:

1. Patients with a loss of B-cell Aplasia within 9 months of first infusion AND are MRD (+) at time of enrollment
2. Patients with a loss of B cell aplasia very early (<3months), early (≤ 3 to <6months) and later (≥6 months) following first infusion

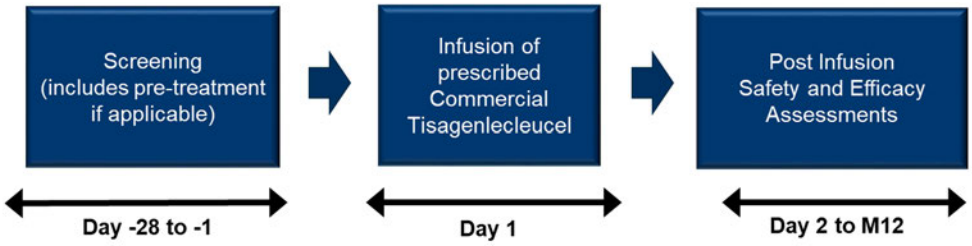
The study will have the following sequential phases for all patients: Screening (Section 8.1.1), Treatment and Follow-up (Section 8.1.5). The total duration of the study is about 12 months. After tisagenlecleucel re-infusion, efficacy will be assessed at months 1, 3, 6, and 12. Safety will be assessed throughout the study.

The end of the study will be when all patients complete a month 12 visit unless discontinuing prior as outlined in Section 9.1. The patient may voluntarily withdraw from the study for any reason, at any time. Patients who receive commercial tisagenlecleucel must be followed for up to 15 years post-infusion. Patients can be followed under the Center for International Blood and Marrow Transplant Research (CIBMTR) cellular therapy registry if consented for participation. For patients who do not provide consent for participation in the Center for International Blood

[redacted]

and Marrow Transplant Research (CIBMTR) registry, AEs will need to be reported as outlined in Table 16-1 per the Safety Reporting guidelines of 15 years or until the patient enrolls in the registry.

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

4.1.1 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T-cell proliferation (Dummer et al 2002), a finding that naive T-cells begin to proliferate and differentiate into memory-like T-cells when total numbers of naive T-cells are reduced below a certain threshold (Goldrath 1999, Surh 2000). Host lymphodepletion may enhance the effectiveness of adoptively transferred T-cells (Dummer et al 2002). Homeostatic T-cell proliferation can lead to activation of certain immune cell subsets (King et al 2004), providing a clue to improved anti-tumor responses. T-cells can undergo up to seven rounds of cell division after being deprived of contact with antigen presenting cells (Kaech 2001, van Stipdonk 2001). Lymphodepletion eliminates regulatory T-cells and other competing elements of the immune system that act as "cytokine sinks", enhancing the availability of cytokines such as IL-7 and IL-15 (Klebanoff et al 2005). Data indicates that the increased anti-tumor 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 lymohodepleting regimen with CD19 CAR-T cell therapies. It has been demonstrated that addition of fludarabine to cyclophosphamide increases CAR-T cell expansion and persistence and improves disease free survival rates in adult patients with r/r B-ALL (Turtle et al 2016).

In previous and ongoing studies with tisagenlecleucel most of the patients received lymphodepleting therapy with fludarabine and cyclophophamide and around 20% of DLBCL patients received bendamustine.

[redacted]

4.1.2 Rationale for choice of background therapy

Please refer to Section 1.1

4.2 Rationale for dose/regimen and duration of treatment

The approved dose range for tisagenlecleucel is:

- 0.2 to 5.0×10^6 CAR positive viable T cells / kg for patients $\leq$ 50 kg or
- to 2.5×10^8 CAR-positive viable T cells for patients > 50 kg.

[Refer to the Kymriah Product Information]

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

4.3 Rationale for choice of control drugs

Not applicable

4.4 Purpose and timing of interim analyses

No formal interim analysis will be performed for this study. As required, interim analyses may be performed every six months for publication purpose.

Please refer to Section 12.7 Interim Analysis.

4.5 Risks and benefits

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of tisagenlecleucel induced AEs are provided in Appendix Table 16-1.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. [Refer to the Kymriah Product Information]

As of 26-Mar-2019, tisagenlecleucel has been administered to over 579 patients in clinical trials across the dose ranges tested, and has a well characterized safety profile in pediatric and young adult patients. Overall, it is anticipated that the benefits of tisagenlecleucel therapy, including complete and long-term remissions when compared to the current standards of care, will outweigh the risks in this study.

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

Poor tisagenlecleucel persistence and early loss of B-cell aplasia within 6 months of tisagenlecleucel infusion are associated with higher risk of relapse. Patients with early B-cell recovery usually proceed to other experimental CAR-T cell therapies or allogeneic hematopoietic stem cell transplant (allo-SCT). Allo-SCT is associated with significant morbidity and mortality, particularly in patients who had received prior allo-SCT. Additionally,

[redacted]

subsequent allo-SCT may not be feasible in some patients because of the lack of a suitable donor or ineligibility due to co-morbidities (Crotta 2017).

Reinfusion of one or more additional dose/s of tisagenlecleucel can restore B cell aplasia in some patients with early evidence of poor persistence or B-cell recovery (by extending persistence) and improve durable remission rates (Maude 2016). If successful, patients may not require subsequent therapies and/or allo-SCT.

Data from clinical trials revealed that the baseline pre-infusion disease burden correlates with the severity of CRS; a higher disease burden was significantly associated with severe CRS (Maude 2014). Patients with B-cell recovery without evidence of overt disease relapse are at lower risk for severe CRS and other complications with tisagenlecleucel reinfusion. Although, in the setting of overt relapse, the risk of severe CRS is increased, consistent with reported incidence in the safety section.

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 such as IFNg, IL-6 and TNF are released by activated T cells or activated monocytes/macrophages. Cytokine release syndrome, including fatal or life-threatening events, has been frequently observed after tisagenlecleucel infusion, in particular if associated with concomitant infections. In almost all cases, development of cytokine release syndrome occurred between 1 to 10 days (median onset 3 days) after tisagenlecleucel infusion. The median time to resolution of cytokine release syndrome was 7 days.

CRS shows a wide range of clinical signs and symptoms (Table 4-2) and is graded according to the Lee Criteria (Table 4-1) (Lee et al. 2014). In the setting of more severe CRS following CAR-T-cell therapy, AEs of macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) have also been reported. Both HLH and MAS have similar clinical manifestations as CRS, irrespective of the underlying cause, and encompass a group of severe immunological disorders characterized by hyperactivation of macrophages and lymphocytes, pro-inflammatory cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure (Neelapu et al 2018). Patients, who experienced severe CRS, showed a clinical phenotype that resembles MAS or HLH including high fever, multi-organ dysfunction or CNS disturbances that is further evidenced by similar laboratory findings of abnormal macrophage activation, high serum levels of ferritin, lactate dehydrogenase and soluble CD25, low fibrinogen, and cytokine profile. Thus, HLH/MAS might not only belong to a similar spectrum of hyper-inflammatory disorders as CRS, but could be interpreted as manifestations of CRS of higher severity (Teachey et al 2018).

Risk factors for severe CRS in pediatric and young adult B-ALL patients are high pre-infusion tumor burden, uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infection and early onset of fever or CRS following tisagenlecleucel infusion.

[redacted]

In pediatric ALL and adult DLBCL patients, high tumor burden is a risk factor for developing severe CRS. In the ongoing clinical study B2202 in pediatric and young adult B-cell ALL (N=75), CRS was reported in 77% of patients (47% with Grade 3 or 4). Two deaths occurred within 30 days of tisagenlecleucel infusion: one patient died with CRS and progressive leukaemia and the second patient had resolving CRS with abdominal compartment syndrome, coagulopathy and renal failure when death occurred due to an intracranial haemorrhage. In the ongoing DLBCL clinical study C2201 (N=111), CRS was reported in 58% of patients, (22% with Grade 3 or 4).

Table 4-1 Clinical signs and symptoms associated with CRS (Lee et al 2014)

Organ system	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia

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 6-3

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 adverse reactions

Neurological events, including events indicative of encephalopathy and delirium of non-infectious origin, have been observed in patients following various types of T cell directed

[redacted]

therapy including tisagenlecleucel and other CAR-T cell therapies of other institutions. The pathophysiology for neurological events, in particular in case of late events, 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 obvious predictors of neurologic toxicity. Confounders, such as preceding or newly induced anti-cancer treatment regimens, might be involved.

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 cytokine release syndrome (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 Blood and Marrow Transplantation (ASBMT) 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 4-3) which incorporates key aspects of the mini-mental status exam via the Immune effector Cell-associated Encephalopathy (ICE) score (Table 4-4).

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 events after tisagenlecleucel infusion can be concurrent with CRS, following resolution of CRS or in the absence 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. Delayed onset of neurological events may also occur as CRS is resolving or after CRS has completely resolved.

[redacted]

In pediatric and young adult B-cell ALL patients, manifestations of encephalopathy and/or delirium occurred in 40% of patients (13% were Grade 3; no grade 4 were observed) within 8 weeks after tisagenlecleucel infusion. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 21% of patients (12% were Grade 3 or 4) within 8 weeks after tisagenlecleucel infusion.

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

Table 4-3 Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grading for children (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, and 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)

[redacted]

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

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 (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?					

For the management of neurological adverse reactions see Section 6.6.2.2

4.5.1.3 Infections

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

- Underlying bone marrow disease or dysfunction increases the risk of infections.
- Patient with prolonged and profound immunosuppression are 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.
- B-cell depletion is known to be associated with hypo- or agammaglobulinemia that contributes to the risk.

[redacted]

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

4.5.1.3.1 Viral Reactivation

Patients with active hepatitis B or active hepatitis C or HIV positive have been excluded from clinical studies with tisagenlecleucel. Patients with prior hepatitis B or C have the potential risk of viral reactivation and the risk of fulminant hepatitis, hepatic failure and fatal outcome.

Subjects with active or prior hepatitis B, hepatitis C or HIV confirmed by serology will not be enrolled in the study; for detailed exclusion criteria see Section 5.2, for serology assessment see Table 16-1

A therapeutic strategy for the management of infections 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 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 Prolonged depletion of normal B cells/agammaglobulinemia

Since normal B-cells express CD19, B-cell aplasia is an expected on-target toxicity of a successful CD19-directed CAR T cell therapy, and a useful surrogate reflecting the persistence of CAR T cells and effectiveness of treatment. B-cell aplasia is observed in all responding patients.

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

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

[redacted]

The AEs observed after tisagenlecleucel infusion were managed well by treatment with immunoglobulins.

A therapeutic strategy for the management of B-cell depletion with resulting hypo-gammaglobulinemia is provided in Section 15.

4.5.1.6 Hematopoietic cytopenias not resolved by Day 28

Hematopoietic cytopenias are an on-target effect after tisagenlecleucel infusion and tisagenlecleucel activity also targeting normal B-cells. Prolonged hematocytopenias not resolved by Day 28 are considered a consequence. The etiology of the cytopenias may be either the CAR-T-cell therapy per se or prior anti-cancer treatment, such as chemotherapy (i.e., multiple lines and cycles), radiation, and lymphodepleting chemotherapy or a combination (Brudno and Kochenderfer 2016), exerting cytotoxic effects. Prolonged neutropenia has been associated with increased risk of infection. A therapeutic strategy for the management of hematopoietic cytopenias is provided in Section 6.6.2.2.

4.5.1.7 Febrile neutropenia

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

A therapeutic strategy for the management of febrile neutropenia is provided in Section 6.6.2.7.

4.5.1.8 Hypersensitivity including acute infusion reactions

Hypersensitivity reactions may also occur due to the excipients (such as dimethyl sulfoxide (DMSO) or dextran 40) of the infused solution in which the cells are dispersed. Clinically, hypersensitivity reactions can be classified as 'immediate' or 'delayed' depending on their onset after drug administration (Corominas et al 2014; Limsuwan and Demoly 2010). In principle, immediate reactions including acute infusion reactions occur within less than 1 hour after drug administration and may present in a wide range of symptoms such as fever, chills, nausea, urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, bronchospasm, tachycardia, hypotension, anaphylaxis or anaphylactic shock. Delayed hypersensitivity reactions appear after more than 1 hour and up to several days after drug exposure and could include variable cutaneous symptoms such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, or drug reaction with eosinophilia and systemic symptoms (DRESS) (Averbeck et 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.

[redacted]

A therapeutic strategy for the management of hypersensitivity including acute infusion reactions is provided in Section 6.6.2.8.

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.

4.5.3 Cerebral edema

Fatal cases of cerebral edema, soon after infusion with rapid evolution, have been reported with CAR-T cell therapies other than tisagenlecleucel (CTL019); in five subjects in the ROCKET study evaluating JCAR015 for the treatment of ALL and in one subject in the Zuma-1 study evaluating KTE-19 for the treatment of CLL. The subject in the ZUMA-1 study is described as becoming febrile on Day 1 and progressing from Grade 3 to Grade 4 CRS, refractory to tocilizumab and dexamethasone, by Day 4. Cerebral edema developed on Day 9, was refractory to siltuximab and mannitol, and led to death on Day 11 (Turtle et al 2017).

No fatal cerebral edemas have been reported following tisagenlecleucel infusion in the clinical development program or the post-marketing setting to date that would resemble five fatal events reported for JCAR015.

4.5.3.1 Generation of replication competent lentivirus (RCL)

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

However, an RCL resulting from manufacturing is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL thus patients will only receive cell products that meet RCL release criteria considered sufficient to confirm the absence of RCL in tisagenlecleucel and the negligible probability of *de novo* generation of any RCL.As per guidance for gene therapy medicinal products, patients exposed to tisagenlecleucel will be monitored for 15 years following last treatment for vectors persistence. RCL is not specifically being evaluated in the CIBMTR or EBMT Cellular Therapy Registry (Novartis Study CCTL019B2401) for long term follow up; however, pharmacovigilance for potential consequences (e.g. malignancies, autoimmune diseases) will be reported.

The management of this potential risk is addressed in Section 6.6.

4.5.3.2 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 (Friedman et al 2010). The rate of new malignancy

[redacted]

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 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 (UPenn) / Children's Hospital of Philadelphia with CTL019 as manufactured by UPenn. 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. can be considered low with the current Novartis manufacturing process.

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

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

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

[redacted]

The management of this potential risk is addressed in Section 6.6

4.5.3.3 New occurrence or exacerbation of an autoimmune disorder

An emerging number and variety of autoimmune diseases following after anti-cancer treatment including immunotherapy are reported, ranging from asymptomatic immunological alterations to life-threatening systemic autoimmune diseases (Pérez-De-Lis et al 2017). However, specific etiopathogenic mechanisms that could clearly link the induced autoimmune disorder with the immunological pathways altered by the anti-cancer treatments are not well understood. Persistent immune abnormalities after treatment with chemotherapy, development of auto-antibodies and neoantigens are proposed to be crucial in the pathogenesis of autoimmune diseases post anti-cancer treatment (Descotes and Gouraud 2008, Chang and Gershwin 2010, Amos et al 2011).

The risk of autoimmune reaction with tisagenlecleucel is low since CD19 is not present on most normal tissue other than normal B-cells. New occurrence or exacerbation of an autoimmune disorder has not been observed with tisagenlecleucel thus far.

4.5.3.4 Hematologic disorders (incl. aplastic anemia and bone marrow failure)

There is potential risk of a hematologic disorder such as 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.

4.5.3.5 Aggravation of graft versus host disease (GVHD)

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

For the management of GVHD see Section 6.6.2.11

4.5.3.6 Transmission of infections agents

Transmission of infections 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 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

[redacted]

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.

4.5.3.7 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 [Kymriah Package Insert].

4.5.4 Other risks

4.5.4.1 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. The human placenta forms an incomplete barrier for blood cells, allowing bidirectional passage of nucleated blood cells. Circulating maternal cells transfer to the fetus during pregnancy, where they may integrate with the fetal immune and organ systems, creating a state of maternal microchimerism (MMc) (Loubiere et al 2006, Stevens 2016). Hence, there is a potential risk that immunologically active maternal tisagenlecleucel positive T-cells may cross the placenta. Currently, the potential impact of tisagenlecleucel on the offspring's B-cells such as inducing B-cell lymphocytopenia or other potential toxicities such as effects on the development of autoimmune disease (see below) is not known.

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.

[redacted]

5 Population

The target population consists of pediatric and adolescent young adult patients up to and including 25 years of age with B-cell ALL who have been previously infused once with tisagenlecleucel and have a loss of B-cell aplasia. Approximately 54 subjects will be enrolled to allow 49 subjects treated.

The investigator or designee must ensure that only subjects 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

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

1. Must have an additional dose of unexpired, commercial tisagenlecleucel available and prescribed by a physician in the course of medical practice.
2. Signed informed consent must be obtained prior to participation in the study.
3. Age up to and including 25 years at the time of ICF signature
4. Patients must have CD-19+ Leukemia
5. Karnofsky (age ≥16 years) or Lansky (age < 16 years) performance status ≥ 50 at screening
6. Patients who were previously treated with commercial tisagenlecleucel and present with evidence of B-cell recovery as defined by:
   a. Peripheral blood (PB) absolute B lymphocyte count ≥ 50/μL, **OR**
   b. PB B lymphocyte ≥ 10% of the total lymphocytes
7. Subjects must meet the following hematological values without transfusion at Screening:
   - Absolute neutrophil count (ANC) ≥ 1,000/mm^3 (≥ 1×10^9/L)
   - Absolute lymphocyte count (ALC) > 300/mm^3 (> 0.3×10^9/L)
   - Absolute number of CD3+ T cells > 150/mm^3 (> 0.15×10^9/L)
   - Platelets ≥ 50 000/mm^3 (≥ 50×10^9/L)
   - Hemoglobin ≥ 8.0 g/dl (≥ 4.9 mmol/L)
8. A serum creatinine of ≤ 1.5 times ULN or eGFR ≥ 60 mL/min/1.73 m^2
9. Adequate pulmonary function defined as:
   - No or mild dyspnea (≤ Grade 1)
   - Oxygen saturation measured by pulse oximetry > 90% on room air
10. Liver function tests including the following:
    - ALT or AST ≤ 5 times the ULN
    - Total bilirubin < 2mg/dl (with the exception of subjects with Gilbert's syndrome. Subjects with Gilbert's syndrome may be included if their total bilirubin is < 4mg/dl).

5.2 Exclusion criteria

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

1. Prior gene therapy other than tisagenlecleucel

[redacted]

2. Prior adoptive T cell therapy other than tisagenlecleucel
3. Active CNS involvement by malignancy
4. Systemic chemotherapy or radiotherapy within 2 weeks prior to enrolment or tyrosine kinase inhibitors (for patients with Philadelphia chromosome positive ALL) within 1 week prior to enrolment.

   Notes:
   - Non-hematologic toxicity from prior treatment must be resolved to CTCAE grade 1 or better.
   - The use of hydroxyurea is permitted for temporary control of WBC elevations in patients with aggressive disease both prior and during the first 7 days after enrolment.
   - The use of corticosteroids within one week prior to enrolment is also allowed
5. Presence of active or prior hepatitis B or C as indicated by serology (for detailed criteria see Table 16-2). Serology must be repeated, if the interval between testing at Screening and tisagenlecleucel infusion exceeds 8 weeks.
6. HIV positivity as indicated by serology. Serology must be repeated, if the interval between testing at screening and tisagenlecleucel infusion exceeds 8 weeks.
7. Clinically significant acute infection confirmed by clinical evidence, imaging, or positive laboratory tests within 72 hrs prior to tisagenlecleucel infusion (e.g., blood cultures, PCR for DNA/RNA, etc.).
8. Previous or concurrent malignancy except for curatively treated non-melanoma skin cancers, in situ carcinoma (e.g. cervix, breast, bladder, prostate), and cancers in complete remission for at least 3 years and without evidence of recurrence.
9. Pregnant or nursing (lactating) women. NOTE: Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours before lymphodepletion (if performed) and prior to tisagenlecleucel infusion.
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they agree to use 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 (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject

[redacted]

- 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 enrollment into this study.

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

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

11. Sexually active males must 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. 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.
12. Known hypersensitivity to the excipients of tisagenlecleucel or to any product to be given to the patient as per the study protocol (e.g. tocilizumab and lymphodepleting agents)
13. Any study procedure (e.g., lumbar puncture) that, in the investigator's judgment and/or according to clinical standards, is a contraindication to participation in the study.
14. Cardiac disorders including

- Unstable angina and/or myocardial infarction within 6 months prior to screening
- History of myocardial infarction (MI), unstable angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to screening
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
- LVEF <45% as determined by ECHO or MRA or MUGA
- NYHA functional class III or IV (Chavey et al 2001)

15. Subjects enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies

[redacted]

6 Treatment

6.1 Study treatment

A second dose of commercial tisagenlecleucel is not considered study treatment because it is released commercially to the treating physician when it is prescribed in the course of medical practice. The doses available for reinfusion were previously manufactured for each individual patient as commercial product and a physician can request an additional dose for commercial release at any time, prior to product expiration and subject to availability.

Tisagenlecleucel is an autologous cellular immunotherapy product that is comprised of CD3+ T-cells that have undergone *ex vivo* T-cell activation, gene modification, expansion and formulation in infusible cryomedia. The transgene to be expressed via lentiviral vector transduction is a CAR targeted against the CD19 antigen. The CAR contains a murine scFv that targets CD19 linked to a transmembrane region derived from the CD8 receptor, which is linked to an intracellular bipartite signaling chain of TCR-ζ (or CD3-ζ) and 4-1BB intracellular signaling domains. The extracellular scFv with specificity for CD19 is derived from a mouse monoclonal antibody. T-cells which are enriched from a 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. Tisagenlecleucel will be expanded *ex vivo*. At the end of the culture, the tisagenlecleucel is 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 [Kymriah Package Insert] and the current version of the [tisagenlecleucel Investigator's Brochure].

Table 6-1 Drug Supply

Drug	***Pharmaceutical Dosage Form***	***Route of Administration***	***Supply Type***	***Sponsor (global or local)***
A Commercially available second dose of tisagenlecleucel prescribed at the discretion of the treating physician in the course of medical practice	Cell dispersion	Intravenous use	Open label, Commercial; infusion bags	Local

6.1.1 Investigational and Control Drugs

Not applicable

[redacted]

6.1.1.1 Decentralized Clinical Trial Model (US sites only)

Not applicable

6.1.1.2 Bio-batch retention samples

Not applicable

6.1.2 Pre-infusion evaluation

If any of the following criteria is met tisagenlecleucel infusion must be delayed until resolution to grade 1. If the period of delay is more than 4 weeks from completing lymphodepletion and there is no significant cytopenia (see Section 6.1.6) Lymphodepletion should be repeated, and these criteria will need to be re-checked prior to tisagenlecleucel infusion.

1. Rapidly progressing primary disease (e.g. leukemia/lymphoma)
2. Clinical evidence of CNS involvement by primary disease
3. Laboratory abnormalities that, in the opinion of the investigator, may impact subject safety or the subjects' ability to receive tisagenlecleucel.
4. Following clinical abnormalities:
   - Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 90% or presence of progressive radiographic abnormalities on chest x-ray
   - Cardiac arrhythmia not controlled with medical management
   - Hypotension requiring vasopressor support
   - Clinically significant active infection confirmed by clinical evidence, imaging, or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, etc.). NOTE: All viral serology must be repeated, if the interval between testing prior to lymphodepletion and tisagenlecleucel infusion exceeds 8 weeks.
5. A significant change in clinical status that would, in the opinion of the investigator, increase the risk of adverse events associated with tisagenlecleucel
6. Toxicities from chemotherapy (including lymphodepletion).
7. Prohibited medications as described in section 6.2.1
8. 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.

[redacted]

9. Live vaccines must not be used in tisagenlecleucel recipients for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during tisagenlecleucel treatment, and until immune recovery following treatment with tisagenlecleucel.
10. Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours prior to tisagenlecleucel infusion.

6.1.3 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 and uric acid. Subjects with elevated uric acid or high tumor burden will receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat).

Infections

Infection prophylaxis with regard to lymphodepletion and other additional treatments should follow local guideline. As appropriate, prophylactic antibiotics should be administered and surveillance testing should be employed prior to and during treatment with tisagenlecleucel.

Cytokine Release Syndrome

Prior to tisagenlecleucel infusion at least 2 doses of tocilizumab per patient (for the first 3 weeks after tisagenlecleucel infusion) must be confirmed as available. Hospitals should have timely access to additional doses of tocilizumab for the management of CRS related adverse events (see Section 6.6.2.1/ Cytokine Release Syndrome (CRS) for details).

Premedication

To minimize potential acute infusion reactions, 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 pre-medication. It is recommended that subjects NOT receive systemic corticosteroids other than physiologic replacement, except for serious emergency, since this may have an adverse effect on tisagenlecleucel expansion and function.

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 6.2.1

[redacted]

6.1.4 Additional study treatments

Lymphodepletion

If patients have a White Blood Cell (WBC) count ≤ 1,000 cells/μL within one week prior to tisagenlecleucel infusion, lymphodepleting chemotherapy is **NOT** required.

The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting regimen.

Tisagenlecleucel should be infused 2 to 14 days after lymphodepletion depending on the lymphodepleting regimen. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion and the WBC count is >1,000cells/μL, the patient should be re-treated with lymphodepleting chemotherapy prior to receiving tisagenlecleucel. 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).

Alternative lymphodepletion for pediatric studies:

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

Female patients of childbearing potential must have a negative pregnancy test within 24 hours prior to the start of lymphodepleting therapy. If the patient does not require lymphodepleting therapy, she should still have a negative pregnancy test at the required visit that takes place 24 hours prior to tisagenlecleucel infusion.**Treatment arms/group**

Not applicable

6.1.6 Guidelines for continuation of treatment

Not applicable

[redacted]

6.1.7 Treatment duration A single dose of tisagenlecleucel will be given within 30 minutes of thawing. For more details please refer to [Kymriah Package Insert].

6.1.8 Tisagenlecleucel dosing regimen

The approved dose range for tisagenlecleucel is: 0.2 to 5.0×10^6 CAR positive viable T cells / kg for patients' $\leq$ 50 kg body weight or 0.1 to 2.5×10^8 CAR-positive viable T cells for patients > 50 kg body weight. For more details please refer to [Kymriah Package Insert].

6.1.8.1 Treatment beyond disease progression

Not applicable

6.2 Other treatment (s)

6.2.1 Concomitant therapy

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 and on the appropriate CRF. During selected trial phases, concomitant medication collection will be modified as outlined in Appendix 2: Tisagenlecleucel Modified Data Reporting and CRF Completion Guidelines (CCGs). Modified collection of concomitant medication information during these periods is designed to capture tisagenlecleucel-related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented.

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

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 including a subject in the study or allowing a new medication to be started. If the subject is already included, contact Novartis/sponsor 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 patients 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 (e.g., events such as febrile neutropenia or hematopoietic cytopenias). Cytokine release syndrome/MAS 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 patients. Revised inpatient data

[redacted]

capture will be utilized for this study to systematically collect subsets of patient data to describe the management of safety events associated with tisagenlecleucel therapy for the purpose of:

- Adequately informing physicians and patients 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.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

Not Applicable

6.2.2 Prohibited medication and non-drug therapies

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

Medication restrictions prior to leukapheresis

Not Applicable

Medication restrictions prior to tisagenlecleucel infusion

1. **Steroids:** Therapeutic doses of steroids must be stopped >72 hours or 5 half-lives, whichever is greater, prior to tisagenlecleucel infusion. However, the following physiological replacement doses of steroids are allowed: <12 mg/m^2/day hydrocortisone or equivalent
2. **Steroids or other immunosuppressant drugs** should NOT be used as pre-medication for tisagenlecleucel therapy (refer to Section 6.2.1/ Pre-Infusion Evaluation) or following tisagenlecleucel infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances. Use of steroids with blood product administration should be avoided just prior to and following tisagenlecleucel if possible or at least minimized.
3. **CNS disease prophylaxis or intrathecal therapy** must be stopped > 1 week prior to tisagenlecleucel infusion (e.g. intrathecal methotrexate)
4. **Radiation therapy** must be stopped > 2 weeks prior to tisagenlecleucel infusion
5. **Investigational therapies** must not be used at any time while on study until the first progression following 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
7. **Granulocyte macrophage-colony stimulating factor** has the potential to worsen CRS symptoms and is not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved. Short acting granulocyte colony stimulating factor (G-CSF)

[redacted]

should not be given 72 hours prior to tisagenlecleucel infusion and long acting G-CSF should not be given 10 days prior to tisagenlecleucel infusion.

8. **Antiproliferative therapies,** other than lymphodepletion including low dose daily or weekly maintenance chemotherapy) should not be used within 2 weeks prior to infusion.
9. Short acting drugs used to treat primary disease (e.g. hydroxyurea) must be stopped > 72 hours prior to tisagenlecleucel.

6.2.3 Rescue medication

Refer to REMS safety and institutional SOPS for neurotoxicity and CRS management.

6.3 Subject numbering, treatment assignment

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 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. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Clinical Data Management System interface.

Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the subject is re-screened. If the subject fails to start treatment for any reason, the reason will be entered into the appropriate CRF page

6.3.2 Treatment assignment

Not applicable

6.4 Treatment blinding

Not applicable

6.5 Dose escalation and dose modification

Not applicable

6.5.1 Dose modifications

6.5.1.1 Tisagenlecleucel dose modifications

Prior to administration of subsequent tisagenlecleucel doses, patient should not experience a significant change in performance or clinical status or laboratory values compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of potential side effects of infusion such as cytokine release syndrome. These patients should have their infusion delayed until the treating investigator determines it is clinically appropriate to

[redacted]

proceed with the tisagenlecleucel infusion. Doses of tisagenlecleucel may be delayed up to 14 days. The dose changes and the reasons should be captured on the CRF.

6.5.1.2 Dose Modifications for comparator drugs

Not applicable

6.5.1.3 Dose adjustments for QTcF prolongation

Not applicable

6.5.2 Follow-up for toxicities

Not applicable

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 (EC) 1394/2007, the Directive 2004/23/EC as well as the rules and principles of the EU "Detailed guidelines on good clinical practice specific to advanced therapy medicinal products." 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 product and the tisagenlecleucel batch, and the link between subject identity and unique subject identifier will be confirmed prior to infusion. The [Kymriah Package Insert] 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

6.6.2 Recommended treatment of adverse events

Patients infused with tisagenlecleucel are at risk of developing a number of AE that are related either to tisagenlecleucel itself, other therapies (e.g. immunochemotherapy) and conditions concurrent with the 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.

[redacted]

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

Patients treated with tisagenlecleucel should not donate blood, organs, tissues, sperm, oocytes and cells.

6.6.2.1 Cytokine Release Syndrome (CRS)

Ensure that at least 2 doses of tocilizumab per patient 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. See full Prescribing Information to use tocilizumab safely and effectively [local Actemra Prescribing Information].

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 patients for signs or symptoms of CRS for at least 4 weeks after treatment with tisagenlecleucel. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. Subjects will be required to remain proximal to the treating site for the first 4 weeks.

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

A recommended treatment algorithm for the management of CRS and the definition of high dose vasopressors is presented below in Table 6-1 and Table 6-3, respectively. The CRS management algorithm is a guideline and the investigator may use discretion or modify the treatment approach as needed for an individual subject.

Table 6-2 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. If neutropenic, administer antibiotics per local guidelines	Not applicable	Not applicable
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	High-flow oxygen Intravenous fluids and high-dose vasopressor/s Treat other organ toxicities as per local guidelines		

[redacted]

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
vasopressors			
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 6-3 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*	Vasopressin + NE ≥ 10 mcg/min*
If on combination vasopressors (not vasopressin)	NE of ≥ 0.2 mcg/kg/min*	NE of ≥ 20 mcg/min*

§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: NE dose (weight-based dosing) = [norepinephrine (mcg/kg/minute)] + [dopamine (mcg/kg/minute) / 2] + [epinephrine (mcg/kg/minute)] + [phenylephrine (mcg/kg/minute) / 10] Reference: Per online institutional guideline by MD Anderson Cancer Center, Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric, dated 30 Jan 2018.

Source: Adapted from Lee et al 2014, Lee et al 2015.

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. Ferritin, CRP and serum cytokine levels should NOT be used for clinical management decisions. Cases of transient left ventricular dysfunction, as assessed by ECHO, have been reported in some subjects with severe (Grade 4) CRS. Therefore consideration should be given

[redacted]

to monitoring cardiac function by ECHO during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

6.6.2.2 Neurological adverse reactions

Neurologic events, primarily reflective of encephalopathy and delirium, may occur after tisagenlecleucel infusion. These present clinically as signs and symptoms of varying severity including: 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. Patients 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
- 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 applicable.
- Chemistry laboratory testing
- EEG

Management

- If the neurological event is concurrent with CRS please refer to Table 6-2. CRS algorithm table for treatment recommendation.
- Consider anti-seizure medications (e.g. 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 (Teachey, et. al 2018, Neelapu et. al 2018).

6.6.2.3 Infections

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

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

Institutional guidelines for vaccination (e.g., pneumococcus) should be followed before starting tisagenlecleucel therapy. As the lack of effective B cells after infusion makes the likelihood of a systemic infection considerable, vaccination with live virus vaccines should not be given for

[redacted]

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

6.6.2.4 Tumor Lysis Syndrome (TLS)

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

6.6.2.5 Prolonged depletion of normal B cells/ hypo- or agammaglobulinemia

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

6.6.2.6 Hematopoietic cytopenias not resolved by day 28

Hematopoietic 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.

Since myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen CRS (if it occurs), these are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.

6.6.2.7 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 4.5.1.3) and CRS (section 6.6.2.1) and managed appropriately with fluids, antibiotics, and supportive care, if applicable.

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

6.6.2.8 Hypersensitivity including acute infusion reactions

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

[redacted]

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

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

6.6.2.9 Generation of replication competent lentivirus (RCL)

The lentiviral vector has been designed to minimize the probability non-homologous recombination, thereby preventing the generation of a RCL, however, this remains a theoretical possibility. It will be detected by blood specimen, e.g., using Vesicular Stomatitis Virus/Glycoprotein (VSV-G) quantitative PCR. If a positive RCL assay result is obtained from a subject, the Investigator will be informed and the subject rescheduled for a retest of the DNA test.

Currently, it is not known, how to manage a subject with confirmed RCL and, therefore, should be addressed on a case by case basis. 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

6.6.2.10 Secondary malignancies (including vector insertion site oligo/monoclonality)

All secondary malignancy should be managed/treated according to current medical practice and local standard of care.

For the follow-up of secondary malignancy, refer to Section 10.2.5

6.6.2.11 Aggravation of graft versus host disease (GVHD)

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

6.6.3 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

For details on the cryopreserved components, and the specific storage and handling requirements of the tisagenlecleucel product, see the [Kymriah Package Insert].

[redacted]

6.7.1 Handling of Tisagenlecleucel

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.

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 patient's identity with the patient 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.

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.

The investigator must maintain an accurate record of the shipment and infusion of commercial tisagenlecleucel for all study participants 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. Please refer to [Kymriah Package Insert] for more information on disposal.

Any used infusion supplies, including the infusion bag(s) and tubing, must be disposed of according to local institutional standard operating procedures. For further details, please refer to the specific guidance provided in the [Kymriah Package Insert]. 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 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 [Kymriah Package Insert].

6.7.2 Handling of additional treatment

Not applicable

7 Informed consent procedures

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

[redacted]

If applicable, in cases where the patient'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 (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH/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 tisagenlecleucel can be found in the Investigator's Brochure (IB) and [Kymriah Package Insert]. This information will be included in the subject informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the tisagenlecleucel that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the 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 patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the required assessments and it is indicated with an “X” at each visit when they are to be performed. All data obtained from these assessments must be supported in the patient’s source documentation. No CRF will be used as a source document. The tables indicate which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) (“Category” column). Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all adverse events and concomitant medications should be recorded on the CRF.

Table 8-1 Assessment Schedule

Period	Category	Screening	Treatment				End of Study
Visit Name		Screening	Enrollment	Assessment Period			End of Study
Day/Week/Month		-28 to -1	D1[1]	D28±7	M3±14	M6±14	M12±14
Obtain informed consent	D	X					
Demography	D	X					
Inclusion/exclusion criteria	D	X					
Relevant medical history/ current medical history	D	X					
Physical Exam	S	X	X	X	X	X	X
Height	D	X					
Weight	D	X	X	X	X	X	X
Vital Signs	D	X	X	X	X	X	X
Karnofsky/Lansky Performance Scales	D	X					X
Serum Pregnancy Test (Table 8-4)	S	X	X				X
Urine Pregnancy Test (Table 8-4)	S			X	X	X	
Hematology	D	X	X	X	X	X	X
Chemistry	D	X	X	X	X	X	X
HIV & Hepatitis B & C testing	D	X					
Serum immunoglobulin levels (IgG, IgA, IgM)	S	X					
Rapid influenza test	D		X[3]				
B & T-Cells by Flow Cytometry – [redacted]	D		X	X	X		X
CTL019 PK by qPCR- NAVIGATE	D		X	X	X		X
[redacted]							
Bone Marrow Aspirate or Biopsy	D	X		X	X[2]	X[2]	X[2]
Re-infusion of prescribed, commercially available tisagenlecleucel	D		X				

[redacted]

Period	Category	Screening	Treatment			End of Study
Visit Name		Screening	Enrollment	Assessment Period		End of Study
Day/Week/Month		-28 to -1	D1[1]	D28±7	M3±14	M6±14	M12±14
Prior/Concomitant Medications	D	X	X	X	X	X	X
Adverse Events (refer to Table 16-1)	D	X	X	X	X	X	X

[1] All Day 1 assessments should be performed prior to infusion with the exception of vital signs which will be monitored before and after infusion
[2] Optional assessments to be performed if clinically indicated
[3] Must be performed within 10 days of infusion during the months of October through May

X = assessment is required
D = assessment to be recorded in clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only

[redacted]

8.1 Study Flow

Please refer to Section 3

8.1.1 Screening

Subjects must sign the IRB/IEC approved informed consent form (ICF) before any study specific screening procedures. Blood tests and assessments to determine eligibility as outlined below will be performed. Screening assessments to determine eligibility should be performed as per the assessment schedule detailed in Table 8-1. Bone marrow biopsy or aspirate to be performed.

Subjects who have signed an informed consent/assent will undergo a routine staging workup (Table 8-1).

The assessments below do not need to be repeated if performed as part of routine clinical care within 4 weeks of the subject signing the ICF:

- Serum immunoglobulin levels (IgG, IgA, IgM)
- Viral tests (EBV, HIV, HbsAg, HBsAb, HBcAb, HCVAb). If HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines (see Appendix 1 for interpretation of Hepatitis B and C results).

8.1.2 Enrollment

For non-randomized trials: the point at which a patient meets all inclusion/exclusion criteria and the patient's additional tisagenlecleucel product is confirmed available at manufacturing facility and prescribed by the treating physician in the course of medical practice.

8.1.3 Leukapheresis

Not applicable

8.1.4 Information to be collected on screening failures

For subjects that fail screening, the following information will be collected:

- Informed Consent Information
- Demography
- Inclusion/ Exclusion Criteria
- Adverse Events (if applicable)
- Death (if applicable)
- Withdrawal of Consent (if applicable)

8.1.5 Treatment

Infusion visit (D1)

On the day prior or day of the scheduled infusion, patients will undergo a physical exam (including weight and vital signs). A blood sample will be collected pre-infusion for PK

[redacted]

assessment, B & T cells by Flow Cytometry [redacted]. In addition, a serum pregnancy test will be performed on women of child bearing potential confirming a negative pregnancy result. Adverse events and prior/concomitant medications will be reviewed.

All patients must undergo a rapid influenza diagnostic test (only during the months of October through May) within 10 days prior to the planned infusion. If the patient is positive for influenza, he/she should complete a full course of oseltamivir phosphate or zanamivir as described on the label (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their full course of treatment **prior** to infusion. The test does not need to be repeated prior to infusion however if influenza sign and symptoms are present, infusion should be delayed until patient is asymptomatic.

For patients that require lymphodepleting chemotherapy, tisagenlecleucel infusion will begin 2 to 14 days after completion. The total window between informed consent and tisagenlecleucel infusion must not exceed 16 weeks.

Tisagenlecleucel transduced T-cells will be given as prescribed and in accordance with the [Kymriah Package Insert]. Vital signs will be monitored before and following infusion. In addition, adverse events and prior/concomitant medications will be reviewed.

For details of assessments, refer to Table 8-1. Visit D28 (±7d)

Patients will undergo blood collection for hematology, chemistry, flow cytometry (B cells, T-cells, and CD19 assessment) [redacted] and CTL019 PK. In addition, patients will undergo a physical exam (including vital signs, weight, and extra medullary disease assessment) and CNS symptom assessments. A bone marrow biopsy or aspirate will be performed. A urine or serum pregnancy test will be performed for females of child bearing potential. A lymph node or tissue aspirate or biopsy may be done if clinically indicated. Adverse events and prior/concomitant medications will be reviewed. For details of assessments, refer to Table 8-1.

Visit M3 (±14d)

Patients will undergo the following: blood collection for hematology, chemistry, flow cytometry (B-cells, T-cells, and CD19 assessment), [redacted] and CTL019 PK, In addition, patients will undergo a physical exam (including vital signs, weight, and extramedullary disease assessment) and CNS symptom assessment. Adverse events and prior/concomitant medications will be reviewed. A urine or serum pregnancy test will be performed for females of child bearing potential. An optional bone marrow biopsy or aspirate to be performed if clinically indicated.

For details of assessments at each visit, refer to Table 8-1.

Visit M6 (±14d)

Patients will undergo the following: blood collection for hematology and chemistry, physical exam (including vital signs, weight, and extramedullary disease assessment) and CNS symptom assessment. Adverse events and prior/concomitant medications will be reviewed. A urine or serum pregnancy test will be performed for females of child bearing potential. An optional bone marrow biopsy or aspirate to be performed if clinically indicated.

[redacted]

For details of assessments at each visit, refer to Table 8-1.

End of Study (EOS)

Visit M12 (±14d)

Patients will undergo the following: blood collection for hematology, chemistry, flow cytometry (B cells, T-cells, and CD19 assessment), [redacted] and CTL019 PK, In addition, patients will undergo a physical exam (including height, weight vital signs, and extramedullary disease assessment), CNS symptom assessment, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. A serum pregnancy test will be performed for females of child bearing potential. An optional bone marrow biopsy or aspirate to be performed if clinically indicated.

For details of assessments, refer to Table 8-1.

Unscheduled Visit

An unscheduled visit may occur at the discretion of the investigator. Assessments will be performed as deemed clinically appropriate, an unscheduled central lab kit will be provided. Adverse events and prior/concomitant medications should be reviewed.

8.1.6 Survival follow-up

Patients are followed on study for 1 year post-second infusion for safety and efficacy evaluations. Investigators are encouraged to report in CIBMTR when appropriate. For a patients enrolled on the CIBMTR Registry CTL019B2401, semiannual and annual evaluations will be performed on all patients who have received a CTL019 cell product infusion as recommended by the FDA and EMA in accordance with the relevant guidelines. All patients who either complete the study or prematurely discontinue post-CTL019 infusion will be enrolled in this destination protocol at the time of study completion/discontinuation (a separate informed consent/assent forms will be provided for this protocol). One to two times a year patients will visit the clinical site for a physical exam and medical history (including concomitant medications and adverse events) with careful attention to features possibly related to lentiviral associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, or new incidence of other hematologic disorders.

8.2 Subject demographics/other baseline characteristics

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

8.2.1 Demographics

The following demographic data will be collected:

- Age
- Gender
- Race

[redacted]

- Ethnicity

8.2.2 Baseline characteristics

The following baseline characteristics will be collected:

- Primary disease
- Medical history
- Prior medication
- Prior antineoplastic therapies
- Prognostic factors
- MRD Status

8.3 Efficacy

Pharmacodynamic and/or clinical samples will be collected at the time-points defined in the Assessment Schedule (Table 8-1).

Efficacy is being measured by

1. B and T-cells by Flow Cytometry
2. CTL019 Pharmacokinetics by qPCR
3. MRD in bone marrow

8.3.1 Efficacy assessments

Efficacy assessments will be performed according to the Novartis guidelines for efficacy evaluation in Acute Lymphoblastic Leukemia studies (Appendix 1), which is based on the NCCN version 1.2013 guidelines, Cheson et al (2003) and Appelbaum et al (2007).

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.

Table 8-2 Assessments & Specifications

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 at screening and infusion. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from the pre-infusion visit except where a complete physical examination is required (see above).

[redacted]

Assessment	Specification
	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 made after informed consent signed which meet the definition of an Adverse Event must be recorded as an adverse event. Assessment of subject reported symptoms suggestive of leukemic involvement of the CNS will be performed and recorded with each physical examination. Examples of CNS symptoms suggestive of leukemic involvement may include, but are not limited to, severe headache or nausea, meningismus or cognitive impairment, without other apparent etiologies.
Vital sign	Vital signs including temperature, BP and pulse measurements. Pulse oximetry will be measured at select visits. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.
Performance Status	Performance status scale shown in Table 8-3 will be used to evaluate the performance status of the subject at visits as described in theTable 8-1.

Table 8-3 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
90	Able to carry on normal activity; minor signs or symptoms of disease	90	Minor restriction in physically strenuous play
80	Normal activity with effort; some signs or symptoms of disease	80	Restricted in strenuous play, tires more easily, otherwise active
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	Ambulatory up to 50% of the time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	50	Considerable assistance required for any active play, fully able to engage in quiet play

[redacted]

Karnofsky Scale (age ≥ 16 years)		Lansky Scale (age < 16 years)	
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	Able to initiate quiet activities
30	Severely disabled; hospital admission is indicated although death not imminent	30	Needs considerable assistance for quiet activity
20	Very sick; hospital admission necessary; active supportive treatment necessary	20	Limited to very passive activity initiated by others (e.g. television)
10	Moribund; fatal processes progressing rapidly	10	Completely disabled, not even passive play
0	Dead	0	Unresponsive

8.4.1 Laboratory evaluations

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Clinically notable laboratory findings are defined in Appendix 2.

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	*Hematocrit*, Hemoglobin, *MCH, MCHC, MCV*, Platelets, *Red blood cells*, White blood cells, *RBC Morphology*, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, *Bands*, Other *(absolute value preferred , %s are acceptable)* ***Assessment will be done locally***
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , *Gamma-glutamyl-transferase (GGT), Bicarbonate*, Calcium, Magnesium, Phosphorus, *Chloride*, Sodium, Potassium, Creatinine, *Creatinine kinase,* Direct Bilirubin, *Indirect Bilirubin*, Total Bilirubin, or Urea ***Assessment will be done locally***
HIV & Hepatitis B & C testing	EBV, HIV, HbsAg, HBsAb, HBcAb, HCVAb ***Assessment will be done locally***
Serum immunoglobulin levels (IgG, IgA, IgM)	IgG, IgA, IgM ***Assessment will be done locally***
CTL019 PK	CTL019 PK by q-PCR and/or flow cytometry (peripheral blood) [redacted]
[redacted]	[redacted]

[redacted]

Test Category	Test Name
B&T cells by Flow cytometry	CD4, CD3, CD8, CD19, CD16+56, CD3+4+8, CD4/CD8 Ratio, CD3/CD19 Ratio [redacted]
Pregnancy Test	Serum pregnancy test performed at Screening, and Pre LD Chemo (Day -14 to Day -2) if applicable, D1 (Pre Infusion), End of Study (Month 12) Urine pregnancy test performed at D28, M3, M6. *A serum pregnancy test can be performed instead of a urine pregnancy test at investigator discretion.* ***Assessment will be done locally***
Rapid Influenza Test	***Assessment will be done locally***

8.4.2 Electrocardiogram (ECG)

Not Applicable

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

Not applicable

8.4.2.2 Cardiac enzymes

Not applicable

8.4.3 Other safety evaluations

Chest X-ray

Not applicable

Imaging

Not applicable

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Clinician Reported Outcomes (ClinRO)

Not applicable

Patient reported outcomes (PRO)

Pediatric Quality of Life inventory – Version 4 (PedsQL™ 4.0)

Not applicable

[redacted]

Trial Feedback

Not applicable

Performance Outcomes (PerfO)

Not applicable

Observer Reported Outcomes (ObsRO)

Not applicable

Proxy Reported Outcomes

Not applicable

8.5.2 Pharmacokinetics

PK samples will be collected at the visits defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the central 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.

Table 8-5 CTL019 pharmacokinetics by q-PCR in peripheral blood collection log

Dose Number Infusion	Day*	Scheduled Time Point*	Tisagenlecleucel Dose Reference ID	PK 1 Tisagenlecleucel Sample No	Sample Volume
2	D1	Pre-dose	201	201	3 mL
2	D28		201	202	3 mL
2	M3		201	203	3 mL
2	M12		201	204	3 mL
2	Unscheduled		201	205	3 mL

[redacted]

[redacted]

8.5.2.1 Pharmacokinetic blood collection and handling

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

8.5.2.2 Analytical method

The assays to be utilized for various PK/biomarker assessments include q-PCR assay to detect CTL019/4-1BB+ cells (transgene copies/microgram DNA) in peripheral blood and other tissues and flow cytometric analysis to detect CTL019 positive cells. Details of sample collections for these assays will be provided in the Central Laboratory Manual.

8.5.3 Biomarkers

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-1).

Follow instructions for sample collection, numbering, processing, and shipment provided in the Central Laboratory Manual.

Quantification of biomarker expression in baseline liquid biopsies will be performed by a central laboratory using quantitative immuno-fluorescence and/or other methods (flow cytometry).

The effect of tisagenlecleucel therapy on B cell levels will be measured in peripheral blood to assess on-target effect on these CD19 positive cells.

[redacted]

8.5.3.1 Additional biomarker assessments

Not applicable

[redacted]

[redacted]

8.5.4 Imaging

Not applicable

8.5.5 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

Patient's participation in the study may be discontinued if, in the investigator's opinion, its continuation would be detrimental to the patient's safety.

Subjects who discontinue from study should NOT be considered withdrawn from the study before they return for the EOS assessments indicated in Section 9.2 Study completion and post-study treatment. If they fail to return for these assessments, every effort (e.g. telephone, email, letter, etc.) should be made to contact them.

Discontinuation of study for a subject occurs when study is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

Study participation must be discontinued under the following circumstances

- Subject/guardian decision
- Investigator Decision
- Pregnancy
- Use of prohibited treatment as per recommendations in section 6.2.2
- Any situation in which study participation might result in a safety risk to the subject
- Any laboratory abnormalities that in the judgment of the investigator, prevents the subject from continuing participation in the study

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

[redacted]

Subjects who discontinue the study or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see section 9.1.2/Withdraw of informed consent section). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

If the subject is willing, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new/concomitant treatments
- adverse events/Serious Adverse Events

9.1.1.1 Replacement policy

Not applicable

Expansion part

Not applicable.

9.1.2 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 allow further collection of personal data

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

Subject's participation in the study must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the 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.

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

[redacted]

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.

9.1.3 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, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of tisagenlecleucel 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 (provide instruction for contacting the subject, when the subject should come for a final visit) 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 a tisagenlecleucel infusion, a long term post-study follow-up for lentiviral vector safety will still continue under a separate destination protocol for 15 years post infusion per health authority guidelines.

The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.1.4.1 Criteria for stopping or pausing the study

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

- The Sponsor 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 tisagenlecleucel

The study may be paused pending notification of the health authorities for investigation and possible protocol amendment if any subject experiences any of the following events within three weeks of the tisagenlecleucel infusion:

- Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to protocol therapy. High fevers, hypotension, hypoxia, disseminated intravascular coagulation, encephalopathy (e.g. lethargy, confusion, aphasia, and seizure), ICU admission, dialysis and mechanical

[redacted]

ventilation are expected. The expected side effects can also result in grade 4 liver toxicity, nephrotoxicity and cardiac dysfunction.

- Death suspected to be related to tisagenlecleucel therapy

9.2 Study completion and post-study treatment

The end of the study is defined as the last visit of the last subject.

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 (e.g., 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 use of a medicinal (investigational) product.

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 adverse events 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 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. The grade according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, with the exception of CRS, which will follow Table 4-2. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe or medically significant, life-threatening and fatal, corresponding to Grades 1 - 5, will be used
2. Its relationship to tisagenlecleucel if the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.

[redacted]

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 tisagenlecleucel.

   All adverse events must be treated appropriately. Treatment may include treatment interruption or withdrawal.
6. Its outcome, i.e., its recovery status or whether it was fatal

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

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 eCRF for medical history.

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 Section 10.1.1.

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

Adverse events separate from the progression of malignancy (e.g., 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 tisagenlecleucel can be found in the [tisagenlecleucel Investigator's Brochure] and [Kymriah package insert].

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.

[redacted]

Detailed AE reporting requirements during the periods of screening, , treatment, follow-up and end of study are outlined in Table 16-1.

Detailed information regarding CRS adverse events (e.g. oxygen requirements, vasopressor usage) will 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 AE [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 (please refer to the ICH-E2D Guidelines).

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:

[redacted]

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

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 occurring after the subject has provided informed consent must be reported to Novartis safety within 24 hours of learning of its occurrence as specified for each study period, including screening, treatment, follow-up and end of study in Table 16-1. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to tisagenlecleucel, 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 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.

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 2.

[redacted]

10.1.6 Pregnancy reporting

Pregnancies

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 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 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 any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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 Tisagenlecleucel errors including misuse/abuse

While commercial tisagenlecleucel will be prescribed to the patients participating in this trial, the procedures for reporting errors in this section will remain applicable and must be followed as outlined in this section.

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.

Treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF 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 including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional 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.

[redacted]

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):

- 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 16-4 in Appendix 3 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-3 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 16-4. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.

If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.

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

1. Serum creatinine increase ≥ 25% compared to baseline during normal hydration status

[redacted]

2. 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, extreme exercise, or trauma)

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

Every renal laboratory trigger or renal event as defined in Table 16-5 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-6 (Appendix 4).

10.2.3 Data Monitoring Committee

Not applicable

10.2.4 Steering Committee

Not applicable

10.2.5 Follow up of Secondary Malignancy

For patients treated with tisagenlecleucel, treating physician/ healthcare providers should contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH if the patient develops a secondary malignancy.

Upon clinical confirmation secondary malignancy, blood samples should be collected for cellular kinetic analysis by qPCR and flow cytometry. Two tubes of blood are requested: 10 ml sample of PBMCs in a sodium heparin collection tube and 6 ml of blood in an EDTA tube.

[redacted].

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 (Table *8-1*) 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.

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

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.

[redacted]

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.

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 classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or 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 delegated CRO 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. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. 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

The data will be analyzed by Novartis and/or a designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Data from all participating centers will be combined, so that an adequate number of patients will be available for analysis. The primary analysis of the study will be performed after all patients have completed the Month 12 visit or prematurely discontinued the study. For this analysis, all primary, secondary [redacted] objectives will be addressed including all variables outlined up to Month 12 and all available safety data. A final Clinical Study Report (CSR) will be produced for the primary analysis of the study.

As required, interim analyses may be performed every six months annually for publication purpose.

12.1 Analysis sets

The analysis sets to be used are defined as below. The Full Analysis Set (FAS) will be used as the primary efficacy analysis set. The Safety Set will be used for all the safety analyses.

All tables and listings will be presented by one treatment arm of CTL019.

12.1.1 Screened Set

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

12.1.2 Enrolled Set

The enrolled set (ENS) comprises all patients who are enrolled in the study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients' additional non-expired dose of tisagenlecleucel has been confirmed available.

12.1.3 Full Analysis Set

The Full Analysis Set FAS comprises all patients whom have received reinfusion of tisagenlecleucel.

12.1.4 Safety Set

The Safety Set comprises all patients who received re-infusion of tisagenlecleucel.

[redacted]

12.1.5 Per-Protocol Set

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

Detailed criteria and determination of major protocol deviations leading to exclusion from PPS will be finalized prior to database lock and primary analysis.

12.1.6 Cellular kinetic analysis set

The Cellular Kinetic Analysis Set (CKAS) consists of all subjects in the FAS who provide evaluable tisagenlecleucel cellular kinetic data. A subject is considered as having evaluable cellular kinetic data if at least one cellular kinetic parameter can be derived. The CKAS will be used for summaries (tables and figures). The FAS will be used for listings of cellular kinetic data.

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

12.1.7 Pharmacokinetic analyses set

The Pharmacokinetic Analysis Set (PKAS) consists of subjects in FAS who have taken at least one dose of the drug and provided at least one PK concentration.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data will be listed by patient and/or summarized descriptively for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented (i.e., mean, median, standard deviation (SD), minimum, maximum).

The number and percentage of patients with prior anti-neoplastic medications/therapies will be summarized.

Relevant medical histories and current medical conditions at baseline will be summarized by primary system organ class (SOC) and preferred term.

12.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, SD, median, minimum, and maximum will be presented.

The total cells infused (cells/kg) and total CTL019 transduced viable T cells infused (cells/kg) will be listed and summarized using descriptive statistics. Patients will be categorized as below, within or above the prescribed dose range.

Prior and concomitant medications and significant non-drug therapies prior to and after the start of re-infusion will be listed by patient and summarized by the Anatomical Therapeutic

[redacted]

Chemical (ATC) term.

12.4 Transfusion during the study will be listed. In addition, whether patients have received anti-cytokine medications for the management of CRS will be summarized.Analysis of the primary endpoint(s)

The primary objective of the study is to evaluate the incidence of B cell aplasia after re-infusion of tisagenlecleucel.

12.4.1 Definition of primary endpoint(s)

The primary endpoint for this study is the proportion of patients who restore B-cell aplasia within 12 months following re-infusion with tisagenlecleucel.

B-cell aplasia is defined as:

- PB absolute B lymphocyte count < 50/μL, AND
- presence of CTL019 cells by qPCR in the peripheral blood

12.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy analysis will be performed on the FAS by testing the following hypothesis:

$$H0: p \leq 0.10 \text{ vs. } HA: p > 0.10$$

The estimated proportion $\hat{p}$ of patients who restore B-cell aplasia within 12 months following re-infusion with the study drug will be presented together with an exact 95% Clopper-Pearson confidence interval (CI).

The null hypothesis (H0) will be rejected if the lower limit of the 95% CI is greater than 0.10, demonstrating improvement after re-infusion.

12.4.3 Handling of missing values/censoring/discontinuations

Patients in the study who are of unknown clinical response will be treated as non-responders. Other missing data are simply noted as missing on appropriate tables/listings.

Patients who proceed to HSCT while in remission after tisagenlecleucel re-infusion will be censored at the time of HSCT.

The volume of missing data generated due to the COVID-19 pandemic may also be assessed and sensitivity analyses will be performed, if deemed appropriate.

12.4.4 Sensitivity and Supportive analyses

In order to assess the robustness of the primary endpoint, sensitivity analyses are planned. These may include, but are not limited to:

- the analysis of the primary endpoint using the PPS
- the analysis of the primary endpoint without censoring for HSCT

As this study is ongoing during the COVID-19 pandemic, the impact of COVID-19 (if any) will be explored on topics such as, but are not limited to, the discontinuation rate, the number of

[redacted]

protocol deviations, disease status, the use of rescue medications, AEs, laboratory values and missing data. As appropriate, a sensitivity analysis of the primary endpoint may be performed to assess the impact of COVID-19, if any, in the study.

12.4.4.1 Subgroup analysis

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

- Age: <10 years, ≥10 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: White, Asian, Other
- Patients with a loss of B-cell Aplasia within 9 months of first infusion AND are MRD (+) at time of enrollment
- Patients with a loss of B cell aplasia very early (<3 months), early (>3 to <6 months) and late (>6 months) following first infusion

As the sample size is small, data will be only summarized within each subgroup.

12.5 Analysis of secondary endpoints

- The secondary efficacy objectives are to evaluate the following: the efficacy of reinfusion of tisagenlecleucel for loss of B cell aplasia as measured by overall remission rate (ORR) 12 months after tisagenlecleucel reinfusion, which includes CR and CR with incomplete blood count recovery (CRi) as determined by investigator assessment for pALL patientsEvaluate event free survival (EFS)
- Evaluate Overall survival (OS)

12.5.1 Overall Remission rate (ORR)

The secondary endpoint is the ORR as determined by investigators assessment during the 12 months after tisagenlecleucel re-infusion. The ORR is defined as the proportion of patients who maintain ORR (= CR + CRi) per Investigator assessment in pALL patients during 12 months post-reinfusion.

The secondary efficacy endpoint, ORR within 12 months of re-infusion, will be analyzed using the FAS. The ORR will be summarized and exact 95% Clopper-Pearson CIs will be reported.

12.5.2 Event free survival (EFS)

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

- Death from any cause after remission
- Relapse
- Treatment failure: Defined as no response in the study and discontinuation from the study due to any of the following reasons:
    - Death
    - Adverse event (including abnormal laboratory values or abnormal test procedure
    - results)

[redacted]

- Lack of efficacy or progressive disease
- New anticancer therapy

In the main analysis of EFS, patients who proceed to SCT after tisagenlecleucel re-infusion will be censored at the time of SCT. In addition, a sensitivity analysis of EFS will be performed without censoring SCT. EFS will be assessed in all patients in the FAS. The distribution function of EFS will be estimated using the Kaplan Meier (KM) method. The median EFS along with 95% confidence intervals will be presented, if appropriate.

12.5.3 Overall survival (OS)

OS is the time from date of tisagenlecleucel re-infusion to the date of death due to any reason. In case a patient is alive at the date of last contact on or before data cut-off, OS is censored at the date of last contact. No censoring will be done in case of SCT. Thus, patients should be followed-up for survival also in case of SCT.

12.5.4 Safety endpoints

12.5.4.1 Analysis set and grouping for the analyses

For all safety analyses, the Safety Set will be used. The overall observation period will be divided into two mutually exclusive segments:

- pre re-infusion period: from day of patient's informed consent/assent to the day before re-infusion of tisagenlecleucel.
- post re-infusion period: starting at day of tisagenlecleucel re-infusion

12.5.4.2 Adverse events (AEs)

Reporting of adverse events will be based on MedDRA and CTCAE version 4.03. Treatment-emergent AEs are defined as AEs that started or worsened after tisagenlecleucel re-infusion. Summary tables for AEs will include only treatment emergent AEs. However, all safety data (including those from the pre re-infusion period) will be listed and those collected during the pre-infusion period are to be flagged. The incidence of treatment-emergent adverse events will be summarized by primary SOC, preferred term, severity (based on CTCAE grades), and relationship to tisagenlecleucel. Patients who experienced multiple AEs for a preferred term will be counted once for that preferred term, similarly for patients with multiple AEs per primary SOC. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of Common Toxicity Criteria (CTC) grade 3 and 4 AEs will be summarized separately.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE.

[redacted]

12.5.4.3 Adverse events of special interest (AESI) are defined by the important identified risk and important potential risk as presented in the effective Risk Management Plan (RMP). MedDRA search criteria to retrieve AEs indicative of these risks are updated on a regular basis at the tisagenlecleucel program level. The most recent version of the AESI search criteria form will be used for the reporting activity. Laboratory abnormalities

- For laboratory tests covered by the CTCAE, the study's biostatistics and reporting team will grade laboratory data accordingly. 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 also be generated separately for hematology and biochemistry: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)

[redacted]

12.5.4.4 B-cell and T-cell level

The levels of B and T cells (peripheral blood prior to and following tisagenlecleucel infusion) will be described. Baseline and absolute and relative change (percent change) from baseline will be calculated and summarized using sample size, mean, standard deviation, median, minimum and maximum. Baseline and change from baseline to minimum cell number may also be summarized by response status and potentially graphed using strip plots. Patient level and averaged cell counts and percent change from baseline may be displayed using longitudinal plots.

It is anticipated that all patients who achieve complete remission will exhibit B-cell aplasia. Timing of B-cell recovery will be summarized. CD8 and CD4 positive T cells will be listed and summarized by time point. Data may also be summarized by response status and potentially graphed using strip plots. Patient level and average longitudinal plots of the cell counts and percent changes from baseline may be generated. For abnormal T cell or B cell results, associated safety events such as infections and use of associated therapies (i.e. antibiotics, immunoglobulin replacement) will be investigated using patient listings. CKAS set will be used for the analysis of [redacted] and biomarkers.

12.5.5 Pharmacokinetics

Plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero for the Pharmacokinetic Analysis Set.

[redacted]

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

12.5.6 Biomarkers

Not applicable

12.5.7 PK/PD relationships

Not applicable

12.5.8 Patient reported outcomes

Not applicable

[redacted]

12.7 Interim analyses

No formal interim analysis will be performed for this study. As required, interim analyses may be performed every six months annually for publication purpose.

12.8 Sample size calculation

This study is an exploratory study to determine the safety and efficacy of tisagenlecleucel re-infusion with an early loss of B-cell aplasia.

Sample size was based on an exact test for single proportion to test the null hypothesis H0: p<=0.10. Where p is the proportion of patients who establish B cell aplasia during 12 months. If the true rate p>= 0.25, then with an one sided alpha level of 2.5% and at least 80% power, a minimum of 49 evaluable patients will be required for the study. Considering drop-out rate of 10%, a total of approximately 54 patients will be enrolled into the study.

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 (e.g., advertisements) and any other written information to be provided to subjects. Prior to study

[redacted]

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

This study only involves healthy volunteers and as such Novartis/sponsor will register the protocol as required to databases specified by local regulations (e.g. EudraCT during CTA filing for studies in EU/EEA). After study completion *(defined as last patient last visit)* and finalization of the study report, results of this trial may be submitted for publication (e.g. peer-reviewed journal) or registered to databases where required by local regulations.

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 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.

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: 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 (2014-2017).

[redacted]

16.2 Appendix 2: Tisagenlecleucel modified data reporting – Treatment and Follow Up Phase

This guidance is used to determine whether or not an AE, SAE, concomitant medication, or laboratory result has to be recorded in the eCRF during the relevant study period. Before using this guidance, the investigator should determine whether or not an AE is serious using the criteria found in the protocol section 10, and then use the applicable row of this guidance to determine whether or not that event is to be recorded in the eCRF.

[redacted]

Table 16-1 Adverse event reporting

	Signed ICF through start of lymphodepleting chemotherapy or re-infusion	**Start of lymphodepleting chemotherapy or re-infusion through Month 12 or discontinuation**
AEs (non-serious and serious)	All AEs grade ≥ 3 All SAEs and deaths All laboratory abnormalities deemed clinically significant by the investigator All infections 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

Table 16-2 Concomitant Medication and Laboratory Reporting

	Screening and Pre-treatment Period (ICF to LD chemo/ re-infusion)	**Treatment and Follow-up Period** (Starting from LD chemo / infusion , through Month 12 or discontinuation)	
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**
Concomitant medications	Modified: **Drugs:**		All

[redacted]

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

[redacted]

	Screening and Pre-treatment Period (ICF to LD chemo/ re-infusion)	**Treatment and Follow-up Period** (Starting from LD chemo / infusion , through Month 12 or discontinuation)	
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**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

[redacted]

Appendix 3: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-3 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 16-4 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study treatment immediately (*if applicable*) Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, TBIL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT, until resolution (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study treatment immediately (*if applicable*) Hospitalize if clinically appropriate Establish causality	ALT, AST, TBIL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

[redacted]

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

[redacted]

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

[a]Elevated ALT/AST > 3 × ULN and 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.

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]

Appendix 4: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-5 Specific Renal Alert Criteria and Actions

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

[+]Corresponds to KDIGO criteria for Acute Kidney Injury

[redacted]

Table 16-6 Follow up of renal events

Assess, document and record in the appropriate CRF

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

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

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

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

or

- Event stabilization: serum creatinine level with ± 10% variability over last 6 months or PCR stabilization at a new level with ± 50% variability over last 6 months
- Analysis of urine markers in samples collected over the course of the renal event

[redacted]