NOVARTIS

Clinical Development

CTL019

Oncology Clinical Trial Protocol CCTL019C2201 / NCT02445248

A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

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List of abbreviations

ABC	Activated B-cell
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
AESI	Adverse events of special interest
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
aPTT	Activated partial thromboplastin time
ASH	American Society of Hematology
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
ATC	Anatomical Therapeutic Chemical
ATG	Anti-Thymocyte Globulin
AUC	Area Under the Curve
[redacted]	[redacted]
BCR	B cell receptor
BiPAP	Bilateral Positive Airway Pressure
BTK	Bruton's Tyrosine kinase
BUN	Blood Urea Nitrogen
CAR	Chimeric antigen receptor
CBC	Complete Blood Count
CCG	CRF Completion Guidelines
CD19 CART	CD 19 redirected autologous T cells
CFR	Code of Federal Regulations
CGD	Chronic granulomatous disease
CGTU	Cell and Gene Therapies Unit
CI	Confidence Interval
CIF	Cumulative incidence function
C_{last}	Last observable concentration
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
C_{max}	Maximum concentration
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
[redacted]	[redacted]
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
[redacted]	[redacted]
CRS	Cytokine Release Syndrome
CSF	Cerebral spinal fluid
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common toxicity criteria

[redacted]

CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T-lymphocyte
CVPF	Cell and Vaccine Production Facility
DFS	Disease free survival
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose Limiting Toxicity
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event free survival
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food & Drug Administration
FDG	Fluorodeoxyglucose
FFP	Fresh frozen plasma
[redacted]	[redacted]
FISH	Fluorescence in situ hybridization
FL	Follicular Lymphoma
FLOW	Flowcytometry
FPFV	First Patient First Visit
GC	Germinal center-like
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
[redacted]	[redacted]
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage-colony stimulating factor
GVHD	Graft versus Host Disease
HA	Health Authority
HBcAb	Hepatitis B core Antibody
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRQoL	Health Relates Quality of Life
HSCT	Hematopoietic stem cell transplantation (refers to both allogenic SCT and autologous SCT)
i.v.	Intravenous(ly)

[redacted]

IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
[redacted]	[redacted]
Ig	Immunoglobulin
[redacted]	[redacted]
IHC	Immunohistochemistry
[redacted]	[redacted]
[redacted]	[redacted]
IN	Investigator Notification
INR	International Normalized Ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
IUD	Intrauterine Device
IWRS	Interactive Web Response System
JCV	John Cunningham Virus
kg	Kilogram
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LDi	Longest transverse diameter of a lesion
LFT	Liver function tests
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
LPLV	Last Patient Last Visit
LSS	Lymphoma specific survival
LTFU	Long Term Follow Up
LTR	Long terminal repeat
LVEF	Left Ventricular Ejection Fraction
MAP	Master Analysis Plan
MAS	Macrophage Activation Syndrome
MCHC	Mean Corpuscular Hemoglobin Concentration
MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Authorities
MHC	Major histocompatibility complex
mL	milliliter
MNC	Mononuclear cell
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
MTD	Maximum Tolerated Dose
MUGA	Multiple Uptake Gated Acquisition
NCCN	National Comprehensive Cancer Network
NE	Norepinephrine Equivalent

[redacted]

NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer cell
NMR	No Metabolic Response
NOS	Not otherwise specified
O_2	Oxygen
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic analysis set
PCR	Polymerase Chain Reaction
PD	Progressive disease
PD	Pharmacodynamics
PE	Physical Examination
PET	Positron emission tomography
PFS	Progression Free Survival
PGS-CRS	The Penn Grading Scale for Cytokine Release Syndrome
PHI	Protected Health Information
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PMBCL	Primary mediastinal large cell lymphoma
PMD	Progressive Metabolic Disease
PML	Progressive Multifocal Leukoencephalopathy
PPD	Product of Perpendicular Diameters
PPS	Per Protocol Set
PR	Partial Response
[redacted]	[redacted]
PT	Preferred Term
PT	Prothrombin time
PTLD	Post-transplant lymphoproliferative disorders
[redacted]	[redacted]
qPCR	Quantitative Polymerase Chain Reaction
r/r	Relapsed or refractory
RAP	Report and Analysis Plan
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RD	Relapsed Disease
RDE	Recommended dose for expansion
REB	Research Ethics Board
RNA	Ribonucleic acid
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SC	Steering Committee
scFv	Single chain variable fragment
SCID-X1	X-linked Severe Combined Immunodeficiency
SCT	Stem cell transplantation
SD	Stable Disease
SDi	Shortest axis perpendicular to LDi
[redacted]	[redacted]

[redacted]

SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOC	System Organ Class
SPD	Sum of the product of the diameters
SUSAR	Suspected unexpected serious adverse reactions
SUV	Standard Uptake Value
TCR	T cell receptors
[redacted]	[redacted]
T_{last}	Time of last observable concentration
TLS	Tumor lysis syndrome
T_{max}	Time to peak concentration
TNC	Total nucleated cells
TNF	Tumor Necrosis Factor
TTF	Time to treatment failure
TTP	Time to progression
TTR	Time to Response
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
UNK	Unknown
UPENN	University of Pennsylvania
VASST	Vasopressin and Septic Shock Trial
V_H	Heavy Chain Variable Domain
V_L	Light Chain Variable Domain
VSV-G	Vesicular Stomatitis Virus, Glycoprotein
WAS	Wiskott-Aldrich syndrome
WBC	White blood cells
WHO	World Health Organization
WOCBP	Women of child bearing potential

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Final Enrollment	Point/time of patient entry into the study when the following have been confirmed: A. ICF signed B. Local patient eligibility confirmed C. Apheresis product reviewed and accepted for manufacturing
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
MAP	Master analysis plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
Subject Number	A unique identifying number assigned to each subject who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
RAP	Report and analysis plan is a regulatory document which provides evidence of preplanned analyses
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including lymphodepleting chemotherapy. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when a patient permanently stops taking study treatment for any reason
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

[redacted]

Amendment 6 (15-Apr-2021)

Amendment Rationale

At the time of this amendment, enrollment to the Main Cohort and Cohort A has been completed. A total of 167 patients were enrolled in the study and 115 patients were infused with CTL019 (99 patients infused in the Main Cohort and 16 patients infused in Cohort A). The last patient was infused on 20-Feb-2018.

As of April 15th, 2021, there are 24 patients on study in the treatment and primary follow-up phase; there are 8 patients on study in the secondary follow-up phase; and there are 3 patients in Survival Follow-up. The rest of the patients are off-study. This amendment 6 will apply to all countries that still have patients on study and in survival follow-up.

The main purpose of this amendment is to:

- Change the required follow-up time of a newborn after live birth from 6 months to 12 months following pregnancy of a female patient or the partner of any male patient. This additional safety monitoring is not due to any new safety concern or emerging data, but is taken on a precautionary basis and aligns with current Novartis internal guidelines.
- Update the protocol safety language to reflect the current Novartis CTL019 program safety language; this includes updates to the Potential Toxicities Section as well as updates to the highly effective contraceptive methods in a newly added Contraception Section. Some of the changes to the Toxicity Section include deletion of Febrile neutropenia, and addition of neurological adverse reactions, viral reactivation, hematological disorders including cytopenias and other changes.
- Add the requirement for urine or serum pregnancy testing at all study visits to align with standard CTL019 monitoring requirements. Changes to the Visit Evaluation Schedule have been made starting at Month 30 and after because all remaining patients are past Month 30 follow-up.
- Add language about secondary malignancies and follow up to align with the CTL019 program standard language.
- Specify that blood samples for RCL testing are banked beyond month 12, as long as all samples through Month 12 were negative.

Given that enrollment is complete, no changes have been made to the inclusion/exclusion criteria, the cytokine release syndrome (CRS) management algorithm and CRS grading scale. Changes to the Visit Evaluation Schedule have been made starting at Month 30 and after because all remaining patients are past Month 30 follow-up. The only change to the Visit Evaluation Schedule is addition of serum or urine pregnancy testing. The contraceptive methods included for WOCBP & males in the inclusion criteria are obsolete and are replaced by those outlined in the newly added Contraception section.

[redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Section 6.2.4.2 General toxicity management considerations: The following sentence has been added: Patients treated with CTL019 should not donate blood, organs, tissues, sperm, oocytes and cells.

Section 6.2.4.2.1 Expected Toxicities: This section has been updated as per the most updated standard program safety language. Febrile Reaction has been deleted. Neurological Adverse Reactions, Viral Reactivation and Hematological disorders including cytopenias have been added.

Section 6.2.4.2.2 Potential Toxicities: This section has been updated as per the most updated standard program safety language.

Section 6.3.2.1 Liver safety monitoring: Table 6-4 and 6-5 have been deleted and replaced by Appendix 5 which contains updated information based on standard program safety language.

Section 6.3.2.2 Follow up on potential drug-induced liver injury (DILI) cases: This section has been added based on standard program safety language.

Section 6.3.2.3 Renal safety monitoring: This section has been added based on standard program safety language.

Section 6.3.3 Anticipated risks and safety concerns: This section has been deleted.

Table 7.1 Primary Visit Evaluation Schedule: Serum or urine pregnancy testing has been added in the Treatment and Primary Follow-up Phase and in the Secondary Follow-up Phase as per standard program safety language. Pregnancies has also been added to the Treatment and Primary Follow-up Phase. Changes to the Visit Evaluation Schedule have been made starting at Month 30 and after because all remaining patients are past Month 30 follow-up.

Section 7.1.3 Treatment and primary follow-up phase: Section has been updated to reflect the addition of urine or serum pregnancy testing added at M30, M36, M42, M48, and M54.

Section 7.1.3.1 End of treatment and primary follow-up (EOT) visit (M60 ±14d) including premature withdrawal: Section has been updated to reflect the addition of serum pregnancy testing added at M60.

Section 7.1.4 Secondary follow-up phase: Section has been updated to reflect the addition of urine or serum pregnancy testing added at M30, M36, M42, M48, and M54. Section has been updated to reflect the addition of serum pregnancy testing at M60.

Table 7.5 Local clinical laboratory parameters collection plan: Updated urine and serum pregnancy testing requirement per standard program safety language.

Table 7.7 CTL019 pharmacokinetics by q-PCR in peripheral blood collection log: A note has been added to clarify that if RCL blood samples test are negative through Month 12, all samples taken after Month 12 will be stored for potential future testing.

Section 8.1.2 Reporting: The following statement has been deleted: infections: defined as bacterial, viral, fungal, or parasitic.

[redacted]

Section 8.2.1 Definitions of SAEs: Section updated to add that All malignant neoplasms (secondary malignancies, not disease progression of the study indication) will be assessed as serious under "medically significant."

Section 8.2.2.3 Month 12 to Month 60: The following sentence has been deleted: 'Defined as bacterial, viral, fungal, or parasite infections'.

Section 8.4 Contraception: The Contraception Section has been added. The contraceptive measures outlined in this section for WOCBP and sexually active males are the effective ones and they replace those presented in the Inclusion Criteria section. Since enrollment is complete, changes to the inclusion criteria have not been made.

Section 8.5 Pregnancies: Section updated per standard program safety language. In case of live birth the newborn will be followed up until 12 months of age (and not 6 months).

Section 8.10 Follow-up of secondary malignancy language has been added as per program standard language.

Section 11.3 Informed Consent Procedures: Section has been updated as per program standard language.

Section 14.3.1 The following sentence has been deleted: 'Defined as bacterial, viral, fungal, or parasite infections'.

Appendix 5: Liver event and Laboratory trigger Definitions and Follow-up Requirements: Appendix 5 has been added with the most updated Liver event and Laboratory trigger Definitions and Follow-up Requirements

Appendix 6: Specific Renal Alert Criteria and Actions and Event Follow-up: Appendix 6 has been added with the most updated Specific Renal Alert Criteria and Actions and Event Follow-up

IRB/IEC

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

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

[redacted]

Summary of previous amendments

Amendment 5 (09-Mar-2017)

Amendment rationale

At the time of this amendment, 144 patients have been enrolled and 95 patients have been treated (92 patients treated in the main cohort (US manufacturing) and 3 patients treated in cohort A (EU manufacturing)). Screening and enrollment to the main cohort was completed. Japanese patients are enrolled only in the main cohort. At the time of enrollment completion in the main cohort, there were 3 Japanese patients enrolled, treated and they are in primary follow-up.

A minimum of 9 Japanese patients must be treated in the study, in order to evaluate the safety and efficacy of CTL019 in the Japanese patient population. This number of Japanese patients is not based on statistical considerations. It will allow the generation of a reasonable data package to support a marketing authorization for CTL019 in Japan. Consequently the protocol is amended in order to allow the enrollment of additional Japanese patients.

With this amendment 5, approximately 10 additional Japanese patients will be enrolled in the main cohort to allow at least 6 additional patients to be treated to ensure a minimum of 9 and maximum of 13 Japanese patients treated with CTL019. The additional Japanese patients will be infused with CTL019 manufactured at the Novartis manufacturing facility in Morris Plains, USA.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Protocol summary was updated to be consistent with other sections of the document.

Section 2.2 Rationale for the study design: Approximately 10 Japanese patients will be added to the previous population, in order to have at least 6 patients treated.

Section 4.1 Description of study design: The description has been updated to include the additional Japanese patients.

IRB/IEC

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

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

[redacted]

Amendment 4 (07-Jul-2016)

Amendment rationale

At the time of this amendment, 72 patients have been enrolled and 29 patients have been treated.

The study has been amended to use PET-CT at baseline and month 3 for primary analysis of response. PET-CT at these time points had already been part of the protocol. With the wide acceptance of metabolic imaging using FDG-PET for staging and response assessment of lymphomas and the recommendations by the International Malignant Lymphomas Imaging Working Group (Cheson et al 2014) this change is considered to improve the diagnostic quality and clinical meaningfulness of the endpoint of ORR in this trial. In the proof of concept study performed at the University of Pennsylvania metabolic response at month 1 and month 3 correlated with duration of response [redacted]. Novartis has revised its guideline for efficacy evaluation in DLBCL and FL studies in version 2 to integrate PET, accordingly. No new imaging assessments were introduced as PET-CT at baseline and at Month 3 was already implemented in the original protocol.

Under the protocol version 03, patients with manufactured cell numbers falling below the target dose and acceptable dose ranges for this study were eligible to receive CTL019 therapy if the product meets all other manufacturing release criteria. Preliminary dose expansion analyses suggest that these very low doses show only minimal in vivo expansion and patients are very unlikely to derive clinical benefit. Consequently, CTL019 doses lower than the protocol specified range will no longer be released.

One additional study cohort was added:

- Cohort A aims to assess efficacy and safety and characterize the *in vivo* cellular PK profile of CTL019 manufactured at the Fraunhofer Institut für Zelltherapie, Leipzig, Germany.

The CRS treatment algorithm was updated with additional details to support trial investigators on appropriate CRS management.

In addition several clarifications have been implemented to ensure protocol adherence.

The changes implemented in this amendment are not impacting the study population of the trial.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Protocol summary was updated to be consistent with other sections of the document.

Section 2.2 Rationale for the study design: One cohort has been added to the previous population (main cohort) to assess the clinical profile of CTL019 manufactured at Fraunhofer Institut für Zelltherapie.

Table 3-1 Objective and related endpoints: Primary objective was clarified as being applicable for the main study cohort only.

Table 3-1 Objectives and related endpoints: PK parameters were updated for the characterization of the in vivo cellular PK profile.

[redacted]

Table 3-1 Objectives and related endpoints: Objectives and endpoints have been added for the new cohort.

[redacted]

Section 4.1 Description of study design: Reference to the response guidance was updated to refer to the [redacted] and the section was updated according to the [redacted].

Section 4.1 Description of study design: Clarification was made that the treatment staggering for new sites is to be considered from infusion rather than from enrollment.

Section 4.1 Description of study design: One cohort has been added to the previous population (main cohort) to assess the clinical profile of CTL019 manufactured at Fraunhofer Institut für Zelltherapie.

Section 4.1.1 Leukapheresis assessment: Wording was updated to remove the cryopreserved aspect of the leukapheresis and that the product should be accepted for manufacturing before shipment to the manufacturing facility.

Section 5.1 Patient population: Figures regarding the patients to be enrolled and treated have been moved to the study design rationale section (section 2.2).

Section 5.2 Inclusion Criteria: Reference to the Cheson Response Criteria was updated to be consistent with other sections of the document.

Section 5.2 Inclusion Criteria: Inclusion criterion 10 language was clarified regarding IUDs

Section 5.2 Inclusion Criteria: Inclusion criterion 11 contraception requirement for male patient with sterile female partner was clarified

Section 5.3 Exclusion criteria: exclusion criterion 7 was further clarified regarding the investigational drug washout period.

Section 5.3 Exclusion criteria: exclusion criterion 8 was further clarified regarding the excluded medications.

Section 6.1.1 Dosing regimen: CTL019 product will no longer be released for infusion if the dose is lower than the specified dose range.

Section 6.1.1.1 Lymphodepleting chemotherapy: Timeframe for the lymphodepleting chemotherapy in relation to CTL019 infusion was clarified to be consistent with section 7.1.2.

Section 6.1.1.1 Lymphodepleting chemotherapy: The need for a negative pregnancy test was clarified.

[redacted]

Section 6.1.1.2 CTL019 Infusion: Criteria for prior therapies that have to be met prior to CTL019 infusion were clarified and rescue medication that should be available at site was further specified.

Section 6.1.3 Rescue medication: Rescue medication that should be available at site was further specified.

Section 6.2.4.2.1 Expected toxicities: Wording regarding Cytokine Release Syndrome (CRS) and CRS Management Algorithm were updated.

Section 6.2.4.2.2 Potential toxicities: Additional information on prevention of hepatitis B reactivation was added

Table 6-1 CTL019 therapy associated grading for cytokine release syndrome: The Penn Grading Scale for Cytokine Release Syndrome (PGS-CRS) was updated.

Section 6.2.6 Concomitant Therapy: Data collection for adverse events and concomitant medications per study period was clarified.

Section 6.2.7 Prohibited concomitant therapy: Wording on excluded medications was clarified to be consistent with other sections of the protocol.

Table 6-5 Liver Event Follow Up Requirements: Wording was clarified to be consistent with study treatment.

Section 6.4.2 Treatment assignment: Wording was clarified.

Section 6.5.2 Drug supply and storage: Reference to the Investigation Product Handling Manual was added.

Section 6.5.3 Study drug compliance and accountability: Reference to the responsible Quality Department was updated.

Section 6.5.4 Study drug disposal and destruction: Wording regarding unused CTL019 product was updated.

Table 7-1 Primary visit evaluation schedule: Lymphodepleting Chemotherapy visit column changed to reflect time window of -W2 to -D5; IRT Registration was clarified to be required at infusion instead of pre-infusion; B-symptoms was changed from infusion to lymphodepleting chemotherapy visit to align with baseline imaging; Wording was added to clarify requirements for baseline imaging within 4 weeks of infusion; Wording was added to clarify D28 bone marrow biopsy only needed if CR and prior bone marrow involvement; Flow cytometry before leukapheresis and on leukapheresis product changed to central; Clarification made that pregnancy test prior to lymphodepleting therapy can be urine or serum; Serum immunoglobulin added at pre-infusion visit and at end of treatment visit; [redacted] CTL019 pharmacokinetics by flow cytometry was added at Month 18 and Month 60; [redacted]

Table 7-2 Secondary follow-up visit evaluation schedule: Removed mentioning of local assessment for flow cytometry in peripheral blood; Survival follow-up phase was further specified as after study completion.

[redacted]

Section 7.1.1 Screening phase: Assessments during the screening phase were updated to clarify accepted assessments performed during screening for study CTL019B2206 or performed as part of clinical routine.

Section 7.1.1.1 Criteria for repeating screening procedures prior to CTL019 infusion: Criteria to repeat screening procedures were clarified.

Section 7.1.1.2 Eligibility screening and enrollment: Enrollment process was clarified and confirmation of infusion in IRT was added.

Section 7.1.2 Pre-treatment phase: Timing of lymphodepleting chemotherapy visit was clarified and assessments to be performed during this visit were further specified. Baseline PET-CT assessment was moved to Lymphodepleting chemotherapy visit to further stress the assessment should be performed as closely before CTL019 infusion as possible.

Section 7.1.3 Infusion visit (D1): B symptom assessment was removed from the infusion visit to align with the baseline imaging assessment. Target dose was clarified to be 5 x 10^8 CTL019 transduced cells.

Section 7.1.3 Post-infusion visit (D28 ±7d): Bone marrow biopsy in patients with CR was clarified to be only required if the patient had prior bone marrow involvement

Section 7.2.1 Efficacy Assessments: Reference to the response guidance was updated to refer to the [redacted].

Section 7.2.1 Efficacy Assessments: Clarification was made that imaging used to determine eligibility must be submitted to the IRC.

Section 7.2.1 Efficacy Assessments: Criteria for use of imaging that was taken prior to ICF was updated to refer to 8 weeks before screening instead of treatment

Section 7.2.1 Efficacy Assessments: Clarification was made that imaging used to determine eligibility must be submitted to the IRC.

Section 7.2.1 Efficacy Assessments: Wording was added to allow for imaging assessments to be completed at any time due to investigator's discretion. Recommendation was made to assess disease status with PET-CT if progression prior to 3 months

Table 7-3 Imaging or disease assessment collection plan: Wording was updated to allow for baseline scan within 4 weeks of CTL019 infusion, without regard to lymphodepleting therapy

Section 7.2.2.2 Vital Signs: Requirement for triplicate blood pressure was removed

Table 7-5 Local laboratory parameters collection plan: Flow cytometry of peripheral blood B cell and T cell levels (secondary follow-up), and flow cytometry on peripheral blood and leukapheresis product was removed to be added as a central assessment

Table 7-6 Central clinical laboratory parameters collection plan: Clarification was made that flow cytometry refers to B and T cells. Flow cytometry on peripheral blood and leukapheresis product was added. Serum immunoglobulin levels was added for secondary follow-up only

Table 7-7 CTL019 pharmacokinetics by q-PCR in peripheral blood collection log: Clarification was made on scheduled time point relative to dosing in order to align with visit evaluation schedule. Unscheduled time point at time of relapse added

[redacted]

Table 7-8 CTL019 pharmacokinetics by flow cytometry in peripheral blood collection log: Clarification was made on scheduled time point relative to dosing in order to align with visit evaluation schedule. Unscheduled time point at time of relapse added

Table 7-12 Immunogenicity serum sample collection log: Unscheduled time point at time of relapse added

Table 7-13 Immunogenicity whole blood sample collection log: Unscheduled time point at time of relapse added

Table 7-14 [redacted] CTL019 Pharmacokinetics (PK), [redacted] treated patients during CRS: Additional time point added at D3 after second dose. Time points added related to 3rd doses and more

Table 7-15 [redacted] CTL019 PK [redacted] treated patients during CRS: New table added

[redacted]

Table 7-17, Table 7-18: Table numbers updated due to new table.

[redacted]

Section 8.1.2 Reporting: Wording on modified data capture for inpatient/in hospital events clarified and reference made to new appendices 3 and 4.

Section 8.2.2.4 Post-treatment protocol: SAE reporting procedure was updated.

Section 8.4 Pregnancies: Requirement for male use of contraception was added to this section as per inclusion criteria 11. Language on IUDs was clarified.

Section 10 Statistical methods and data analysis: Primary analysis clarified to be performed on patients in the main cohort and changed from 6 months to 3 months.

Section 10.1.2 Enrolled Set: Wording updated to specify apheresis product only has to be accepted for manufacturing.

Section 10.1.4 Safety Set: Wording removed stating that the safety set contains the same patients as the full analysis set.

Section 10.1.5 Per-Protocol Set: Clarification was made that missing or incomplete documentation of disease is referring to baseline assessments. Distinction was made between target dose and minimum dose.

Section 10.2 Patient demographics/other baseline characteristics: Updated due to addition of new cohort.

[redacted]

Section 10.3 Treatments (study treatment, concomitant therapies, compliance): Updated due to addition of new cohort.

Section 10.4 Primary Objective: Addition of wording to clarify that the primary objective is related to the main cohort.

Section 10.4.1 Variable: Changes were made to Table 10-1 and the text to describe how to incorporate PET into the overall response assessment as per the [redacted].

Section 10.4.3 Handling of missing values/censoring/discontinuations: Updated reference to Novartis guideline for efficacy evaluation in DLBCL and FL studies based on [redacted].

Section 10.5.2 Other secondary efficacy objectives: Updated due to addition of new cohort.

Section 10.5.2.7 Efficacy in cohort A: Secondary objectives relating to cohort A were added.

Section 10.5.3.4 Immunogenicity updated to be consistent at program level. Section 10.5.3.6 Safety subgroup analysis: Wording was added to clarify that AEs will also be summarized separately for cohort A.

[redacted]

Section 10.5.4 Pharmacokinetics: Wording regarding descriptive statistics of key PK parameters for cohort A was added.

Table 10-2 Noncompartmental pharmacokinetic parameters updated to be consistent at program level.

[redacted]

Section 10.7 Interim Analysis: Wording was updated to specify that the Interim Analysis will be performed on patients in the main cohort when approximately 50 patients have received CTL019 infusion and have completed 3 months from study day 1 infusion or discontinued earlier.

Section 10.8 Sample size calculation: Wording was updated to specify that sample size calculation was performed for the main cohort.

Section 14 Appendix 1: Guidelines for efficacy evaluation in diffuse large B cell lymphoma and follicular lymphoma studies (based on Cheson response criteria) were updated to include [redacted].

Section 14 Appendix 2: Eligibility based on serologic markers for hepatitis B infection: Wording below table was updated for consistency and table was re-ordered for clarity

Section 14.3 Appendix 3: CTL019 modified data reporting – Treatment and Primary Follow Up Phase was added to provide further guidance.

[redacted]

Section 14.4 Appendix 4: CTL019 modified data reporting – Secondary Follow Up Phase was added to provide further guidance.

IRB/IEC

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.

[redacted]

Amendment 3 (18-Dec-2015)

Amendment rationale

The PET-CT was specified to be performed within 4 weeks of infusion but prior to start of lymphodepleting therapy. During the startup of the trial it became evident that the baseline PET-CT required at screening may often be too far out from the actual CTL019 infusion to serve as a valid baseline for subsequent response assessments.

In addition, it was clarified that at least one sentinel vial must be shipped together with the leukapheresis product.

Changes to the protocol

Protocol summary was updated to be consistent with other sections of the document.

Section 4.1 Description of study design: Wording was added to clarify the interpretation of the Day 28 imaging assessment.

Section 4.1.1 Leukapheresis assessment: The timing of leukapheresis was clarified and wording was added regarding shipment of a sample sentinel vial.

Section 5.2 Inclusion criteria: Criterion 8.e. was further specified to define an absolute number of CD3+ cells >150/mm^3. In addition, a note regarding the apheresis product was removed.

Section 5.3 Exclusion criteria: Therapy mentioned under criterion 8 were further specified or removed. Exclusion criterion 18 was removed.

Section 6.1.1.2 CTL019 infusion: Requirements regarding immunosuppressive therapies were updated and wording was revised, for consistency.

Figure 6-2 Progressive Multifocal Leukoencephalopathy (PML): diagnosis and treatment: Figure was modified to include one box “Infectious disease consultation”.

Section 6.2.4.2.2 Potential toxicities: Wording regarding hepatitis reactivation was updated.

Section 6.2.7 Prohibited concomitant therapy: Allowed dose for steroids was updated for consistency.

Table 7-1 Primary visit evaluation schedule: Table was updated to move the PET-CT scan from screening to prior to start of lymphodepleting therapy; the allowed interval was added for D4 and D7 visit; adverse events assessment was updated to be consistent with Section 8.1; HBsAb testing was added to viral serology; CTL019 pharmacokinetics by flow cytometry assessment was added to D1 visit;

Table 7-1 Primary visit evaluation schedule: Two laboratory assessments were added. “Flow cytometry before leukapheresis (peripheral blood)” and “flow cytometry (leukapheresis product)”.

Section 7.1.1 Screening phase: HBsAb testing was added to viral serology.

Section 7.1.1 Screening phase: Wording regarding flow cytometry was added.

Section 7.1.1.1 Criteria for repeating screening procedures prior to CTL019 infusion: Criteria to repeat screening procedures were clarified.

[redacted]

Section 7.1.2 Pretreatment phase: Wording added regarding the PET-CT scan to be performed within four weeks prior to the scheduled infusion.

Section 7.1.3 Treatment and primary follow-up phase: Wording was added to clarify the interpretation of the Day 28 imaging assessment.

Section 7.2.1 Efficacy assessments: Wording was clarified regarding the PET-CT scan to be performed within four weeks prior to the scheduled infusion.

Table 7-3 Imaging or disease assessment collection plan: Wording clarified regarding the PET-CT scan to be performed within four weeks prior to the scheduled infusion.

Section 7.2.2 Safety and tolerability assessments: Wording regarding requirements to repeat assessments during screening was removed due to duplication.

Table 7-5 Local clinical laboratory parameters collection plan: HBsAb assessment was added to viral serology.

Table 7-5 Local clinical laboratory parameters collection plan: Flow cytometry was added as additional assessment.

Table 7-8 CTL019 pharmacokinetics by flow cytometry in peripheral blood collection log: D1 assessment was added and PK sample numbers were updated accordingly.

Table 7-14 [redacted] CTL019 Pharmacokinetics (PK), [redacted] treated patients during CRS: Dose reference ID was added.

[redacted]

Section 8.2.2.4 Post-treatment protocol: Wording regarding long-term follow-up protocol was added for clarification.

Section 10.6.1.2 Data handling of Serum Cytokine Data: Wording was corrected.

Section 13 References: Two references were added.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

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.

[redacted]

Amendment 2 (12-Nov-2015)

Amendment rationale

The protocol was mainly amended to implement clarifications in line with health authority feedback and to incorporate recent experience from the University of Pennsylvania (Penn) study CTL019A2101J/UPCC13413.

The following modifications were implemented in the protocol:

- Histological confirmation of relapse by central pathology review before enrollment was added on health authority request to verify that patients entering the study have histological relapse
- "relapsed/refractory disease after ≥2 lines of chemotherapy …" was defined as "relapsed or refractory disease after ≥2 lines of chemotherapy, including rituximab and anthracycline," to ensure patients will have received prior standard treatment regimen.
- Data generated from clinical samples from study CTL019A2101J/UPCC13413 identified T cell/histiocyte rich large B cell lymphoma (THRBCL) as a subpopulation that is unlikely to derive greater benefit from treatment with CTL019. Therefore, patients with THRBCL will be excluded from this trial.
- Based on one case of encephalitis in study UPCC13413/A2101J the DMC of study CTL019 recommended excluding patients with active neurological or inflammatory or auto immune disorders (e.g. Guillain-Barre Syndrome, Amyotrophic Lateral Sclerosis) from this trial. This exclusion criterion was added accordingly.
- It was clarified that patients with primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), EBV positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma are excluded as they are considered to be separate disease entities.
- [redacted]
- Contraception requirements were also clarified to better define the minimal duration of contraception after infusion.
- Expected toxicities were updated to provide more detailed recommendations for treatment of cytokine release syndrome
- Language regarding liver safety monitoring was added as per current Novartis standard and in order to ensure patients safety and enhance reliability in determining the hepatotoxic potential of an investigational treatment.
- Pharmacokinetics and correlative objectives and endpoints were updated and clarified to better define the specific analysis [redacted]

[redacted]

[redacted]

- In general, the pharmacokinetics [redacted] sections were split for clarification.
- Recommendations on vaccination were added

At time of this amendment seven patients had been enrolled. None of the enrolled patients would have been excluded from the trial had the amendment been in place prior to enrollment. Thus, the current amendment is not expected to influence the study population.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Glossary of terms: the term "final enrollment" was specified.

Protocol summary was updated to be consistent with other sections of the document.

Section 1.2.1 Overview of CTL019: references to the Investigators Brochure were added.

Section 1.2.1.2 Clinical experience: A summary of Clinical Cellular Kinetics (Pharmacokinetics) was added with current data.

Section 2.3 Rationale for dose and regimen selection: Wording was refined for clarification and to differentiate between target dose and allowable dose range.

[redacted]

Section 4.1 Description of study design: Study design was clarified with a more detailed figure.

Section 4.1.1 Apheresis assessment: Apheresis procedure and assessment of apheresis product by Novartis manufacturing was clarified.

Section 4.2 Definition of end of the study: Revision of the wording to align within the document.

Section 5 Population: The patient population was clarified based on feedback from Health Authorities and data generated from study CTL019A2101J/UPCC13413; contraception requirements were updated.

Section 6.1.1 Dosing regimen: A definition of the target dose and a description of the requirements for infusion of doses below the target dose were added.

Section 6.1.1.1 Lymphodepleting chemotherapy: Wording was clarified.

Section 6.1.1.2 CTL019 infusion: Requirements for influenza testing and other criteria to be met before CTL019 infusion were clarified; requirements for infusion of doses below the target dose were added to align within the document.

Section 6.1.3 Rescue medication: Rescue medication that should be available at site was further specified.

[redacted]

Section 6.2.4.2.1 Expected toxicities: A recommendation for cardiac monitoring during management of Cytokine Release Syndrome (CRS) was added, the CRS Management Algorithm was updated to provide additional guidance and a recommendation for vaccination was added.

Section 6.2.4.2.2 Potential toxicities: Wording was clarified and recommendations on hepatitis B reactivation were added.

Section 6.2.7 Prohibited concomitant therapy: time interval for steroids and anti-proliferative therapies prior to infusion was clarified.

Section 6.3.2 Follow-up for toxicities: A section for liver safety monitoring was added.

Section 6.5.1 Study drug packaging and labeling: Wording was clarified.

Section 6.5.3 Study drug compliance and accountability: Wording was clarified.

Section 7.1 Study flow and visit schedule: Columns and assessments in Tables 7-1 and 7-2 were clarified.

Table 7-1 Primary visit and evaluation schedule: Wording on Hepatitis B reactivation was removed as it was a duplication of Section 6.2.4.2.2. Lines for Leukapheresis pre-evaluation and acceptance, [redacted] sample descriptions for PK [redacted] samples were clarified; HBcAb testing was added to viral serology.

Section 7.1.1 Screening phase: Assessments to be performed during the screening phase were clarified and aligned with other sections of the document and criteria to repeat screening procedures prior to CTL019 infusion were aligned with Section 7.2.2.

Section 7.1.2 Pre-treatment phase: Wording regarding lymphodepleting therapy was clarified.

Section 7.1.3 Treatment and primary follow-up phase: Requirements to perform a tumor biopsy were clarified.

Section 7.1.5 Survival follow-up phase: Wording was revised for clarification.

Table 7-3 Imaging or disease assessment collection plan: Wording was further specified.

Section 7.2.2.5 Laboratory evaluations: Wording was revised for clarification.

Section 7.2.3 Cellular Kinetics and Pharmacokinetics: Clarifications and updated sample numbers were added to sample collection log tables, [redacted]

Section 8.1.4 Adverse events of special interest: Neurotoxicity and hepatic events were added to the section.

Section 8.2.2.3 Serious Adverse Event Reporting: Criteria for expedited SAE reporting were added.

[redacted]

Section 8.4 Pregnancies: Contraception requirements were updated.

[redacted]

Section 10.4.4.1 Subgroup analysis: Criteria for subgroup analyses were clarified.

Section 10.5.2.1 Duration of overall response (DOR): Optional additional data summary was added.

Section 10.5.2.6 Efficacy in histological and molecular subgroups: subgroup of T-cell histiocytic-rich large B-cell lymphoma was removed due to exclusion of this subgroup.

Section 10.5.3.4 Immunogenicity: Wording was revised for clarification

Section 10.5.3.6 Safety subgroup analysis: subgroup of T-cell histiocytic-rich large B-cell lymphoma was removed due to exclusion of this subgroup.

Section 10.5.4 Pharmacokinetics: Wording was revised for clarification.

Section 10.6.1 Wording was revised for clarification.

Section 10.6.1.3 Basic Tables, Listings and Figures: Wording was revised for clarification.

[redacted]

Section 10.6.4 Efficacy in sub-populations: EFS was added as endpoint for the analysis.

[redacted]

Section 14.1 Guidelines for efficacy evaluation in DLBCL and FL studies: Analysis of PET results was specified.

IRB/IEC

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.

[redacted]

Amendment 1

Amendment rationale

As of February 2015, this study has not been initiated at any site. The main changes in the amendment are as follows:

An interim analysis was added once the first DLBCL 50 patients have been treated and followed up for 6 months. Based on the α-spending function according to Lan-DeMets (O'Brien-Fleming), if the lower bound of 99.08% exact confidence interval for ORR is greater than 20% then statistical significance can be declared. If the predicted probability of success (i.e., positive result at the end of the study) is less than 10% then the study may be terminated due to futility.

At the beginning of the trial, a safety run-in stage will be conducted to enroll at least three patients to assess the acute safety profile and product characteristics of the Novartis manufactured CTL019 cell product.

[redacted]

The inclusion and exclusion criteria have been modified to ensure a homogenous population.

Language in the protocol has been changed to be consistent with the approved CTL019 standard protocol language and protocol language associated with discontinuation from the clinical trial has also been updated.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined font for insertions.

Section 1.2.1 Overview of CTL019: 2nd paragraph re-written to be consistent with agreed upon CTL019 standard protocol language. Updated reference (Maude et al 2014) added

Section 1.2.1.2 Clinical experience: Updated reference (Maude et al 2014) added. Table 1-1 Summary of ongoing human studies, updated with additional information from July 2014 to January 2015.

Section 2.1 Study rationale and purpose: Updated information from the University of Pennsylvania phase II lymphoma study added

Section 2.2 Rationale for the study design: Bendamustine added as a lymphodepleting chemotherapy option for those patients with cyclophosphamide resistance, language added to clarify that patients who either complete or discontinue from the primary follow-up phase will have an End of Treatment and Primary Follow-Up Visit. Language added for which section to refer to for more information on expected toxicities. Language added to indicate all patients will be asked to consent to the LTFU study. Language added for safety run-in stage.

Section 2.2.1 Rationale for lymphodepletion: Updated information from ongoing CTL019 trials included in regards to lymphodepleting chemotherapy.

Section 2.3 Rationale for dose regimen and selection: Updated information in regards to Cytokine Release Syndrome (CRS) and neurologic disturbances added.

[redacted]

Section 3 Objectives and endpoints: Changes have been made to further explain and clarify the intended study objectives and endpoints in Table 3-1. Evaluate efficacy and safety in histological and molecular subgroups added as a secondary objective. The secondary objective "characterize the in vivo cellular PK profile" has been updated to indicate as summarized by clinical response, corresponding endpoint updated for clarification. [redacted] Specific histological subtypes added to secondary objective analysis. [redacted]

Section 4.1 Description of study design: Language added to indicate reason why CT/MRI, PET-CT have been added to study design. Description of safety run-in stage added.

[redacted]

Section 4.2 Definition of end of the study: New paragraph added to document that patients who discontinue from the primary follow-up phase will continue to be followed in the secondary follow-up phase to collect health authority requested data. Language added to indicate survival follow-up can be conducted via a form or by telephone contact.

Section 4.3 Early study termination: New discontinuation language added to protocol

Section 5.1 Patient population: Clarification to indicate approximately 100 patients enrolled to allow for 80 patients to be treated added

Section 5.2 Inclusion criteria: At last relapse removed from inclusion criterion #3 and criterion #3 updated to clarify DLBCL to be histologically confirmed by local pathology. Allogeneic HSCT removed from inclusion criteria #4. Absolute lymphocyte count (ALC) $\geq 300/mm^3$ added to criterion #8. 8a eGFR criterion modified and without transfusion removed from criterion 8e. Criterion #9 clarified to indicate must have an apheresis product accepted for manufacturing.

Section 5.3 Exclusion criteria: Histology other than DLBCL present on biopsy sample, and transformed indolent NHL or CLL and allogeneic HSCT removed as exclusion criteria. Chemotherapy and radiation therapy exclusion changed from 4 weeks prior to enrollment to 2 weeks. Language added to clarify that chemotherapy other than lymphodepleting chemotherapy within 2 weeks of enrollment is an exclusion criterion. Language added to clarify that HIV positive patients are excluded from the study.

Section 6.1.1.2 CTL019 infusion: section modified to be consistent with CTL019 standard protocol language, including criteria to be met prior to infusion, infusion time and what to do with unused supplies. Criteria #5 updated to be consistent with DLBCL criteria. Language

[redacted]

added to indicate a study physician must evaluate the patient prior to infusion. Infusion time interval for CTL019 injection removed.

Section 6.1.3 Rescue medication: [redacted] Language added to indicate steroids given to treat CRS must be listed on the concomitant medication CRF.

Section 6.1.5 Treatment duration: infusion time interval of 2-20 minutes removed

Section 6.2.4.1.1 Criteria for stopping or pausing the study: Section modified to be consistent with CTl019 standard protocol language, no new information included and language added about stopping or pausing the study during the safety run-in stage added.

Section 6.2.4.2.1 Expected toxicities: Updated information from study UP13413 in regards to CRS added. Table 6-2 High dose vasopressor use, dosing information updated

Section 6.4.1 Patient numbering: Clarification provided to indicate center number is four digit followed by a three digit patient number

Section 6.5.3 Study drug compliance and accountability: Section updated to be consistent with CTL019 standard protocol language

Section 6.5.3.2 Study drug accountability: Verbiage deleted and added to section 6.5.3 to be consistent with CTL019 standard protocol language

Section 6.5.4 Study drug disposal and destruction: Section title updated and additional language added to refer to product handling manual

Section 7.1 Study flow and visit schedule: Table 7-1 Primary visit evaluation schedule has been updated. Antineoplastic therapies after CTL019 infusion indicated after D2 until M60. Imaging updated to indicate at M3 if no PET CT and M6. Language added to CRS assessments to indicate to refer to additional tables in protocol. Language added to clarify peripheral blood assessments. CTL019 pharmacokinetics by flow cytometry (peripheral blood) added as a study assessment. [redacted] CTL019 PK by flow cytometry removed from Peripheral blood-central assessment, additional peripheral blood central assessment added at day 11. [redacted] Survival follow-up updated to start after day 2.

Section 7.1.1 Screening phase: Clarification provided to indicate central pathology assessment and central subtype determination not part of the medical history. Language added to clarify FDG PET should be a dedicated machine. Language added to viral serology to indicate that if the HIV test is positive at screening than a confirmatory HIV test is to be performed as per current local guidelines.

Section 7.1.1.1 Rescreening: ECHO/MUGA to be repeated after 6 weeks, and additional clarifications per the CTL019 standard protocol language added.

Section 7.1.1.2 Eligibility screening and enrollment: Verbiage has been removed in regards to confirming clinical eligibility since this will be done via IRT.

[redacted]

Section 7.1.2 Pre-treatment phase: Section updated to be consistent with CTL019 standard protocol language and also clarifications on timing intervals for lymphodepleting chemotherapy updated for DLBCL patients. Language added to indicate that additional frozen samples from the apheresis material as well as the CTL019 product will be collected at the manufacturing site for correlative studies.

Section 7.1.3 Treatment and primary follow-up phase: [redacted] Language added to clarify FDG PET should be a dedicated machine at the site. Additional language added for clarification on survival follow-up every 3 months.

Section 7.1.3.1 End of treatment and primary follow-up (EOT) visit (M60 ±14d) including premature withdrawal: Language added to indicate that the patient will be followed for survival until the end of this study or the patient enrolled in the long term follow-up (LTFU) study, whichever comes first.

Section 7.1.4.1 Criteria for premature patient withdrawal from the study: Language added to provide additional information on research results and biological samples.

Section 7.1.5 Survival follow-up phase: Language added to indicate survival status can be obtained via phone contact

Section 7.1.7 Discontinuation of study treatment: Section added to be consistent with new discontinuation language.

Section 7.1.8 Withdrawal of consent: Section added to be consistent with new discontinuation language.

Section 7.1.9 Follow-up for safety evaluations: Section added to be consistent with new discontinuation language.

Section 7.1.10 Lost to follow-up: Section added to be consistent with new discontinuation language.

Section 7.2.1 Efficacy assessments: Clarification added that efficacy evaluation will be done in all lymphomas, not just DLBCL. Language added to describe process to be followed for radiological imaging and what will be centrally reviewed by the IRC. Language added to clarify central lab is responsible for pathology assessment and molecular subtype determination. Randomization changed to enrollment. Language added to indicate acceptable imaging modalities for the study.

Section 7.2.2.1 Physical examination: Wrong CRF page originally indicated, updated with correct CRF page

Section 7.2.2.5 Laboratory evaluations: Table 7-5 updated to indicate if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines. [redacted]

[redacted]

Section 7.2.3 Pharmacokinetics: Table 7-7 updated with additional clarifications. A new table inserted for CTL019 pharmacokinetics by flow cytometry in peripheral blood collection log. Sample volume updated in Table 7-12 from 6 mL to 10 mL. Table 7-14 [redacted] CTL019 PK [redacted] treated patients updated. [redacted] Language removed to indicate that the D-1 aliquot will be collected pre-infusion.

[redacted]

Section 8.1.2 Reporting: The word "documented" deleted to indicate all infections are to be recorded in adverse events CRF. Language added to clarify that regardless of causality all lab abnormalities deemed clinically significant, will be recorded in the Adverse Events CRF. Language added to indicate within 28 days after CL019 infusion patients will require multiple days of ICU care

Section 8.1.4 Adverse events of special interest: Language added to indicate that adverse events of special interest may require further investigation. Clarification in regards to current defined AESIs for CTL019 and definitions may be updated as new data arises.

Section 8.2.2 Reporting: Section updated to be consistent with approved CTL019 standard protocol language, reporting procedures are now clarified by what is required at the different study phases, screening/pre-treatment, study-related treatment to Month 12, Month 12 to Month 60, and post-treatment.

Section 8.4 Pregnancies: Language added to clarify that each pregnancy occurring once patient has been infused with CTL019 must be reported within 24 hours. Language updated to be consistent with the approved CTL019 standard protocol language. In case of live birth, newborns will now be followed for 6 months instead of 3.

Section 8.6 Data Monitoring Committee: language added to section to indicate DMC will review data related to interim analysis and safety data at regular intervals.

Section 10.4.1 Variable: change has been made in regards to best overall disease response of progressive disease from 12 weeks to 14 weeks after CTL019 infusion as per the Novartis modified Cheson criteria.

Section 10.5.2.2 Event free survival (EFS): Adequate assessments no longer available added as a censoring reason.

Section 10.5.2.6 Efficacy in histological and molecular subgroups: Section added for clarification.

Section 10.5.3.2 Adverse Events (AEs): Section indicated that AESIs will be updated prior to reporting and Table 10-2 removed

[redacted]

Section 10.5.3.6 Safety subgroup analysis: histological and molecular subgroups added to analysis

Section 10.5.4 Pharmacokinetics: Updated to include language about what q-PCR generated CTL019 concentrations will be displayed graphically. "Mass x time x volume -1" removed from Table 10-2 noncompartmental pharmacokinetic parameters. [redacted]

Section 10.6.1.3 Basic Tables, Listings and Figures: Language about CTL019 protein detection reagent removed. Language about analysis of leukocyte transcriptome analysis added.

[redacted]

Section 10.7 Interim analysis: New section to protocol amendment, an interim analysis has been added when approximately 50 of the planned 80 patients have received their infusion and completed 6 months from study day 1 infusion or discontinued earlier. Table 10-3 included to describe the simulated scenarios for interim analysis and final analysis.

Section 10.8 Sample size calculation: Language updated to clarify the rationale for sample size calculation

Section 13 References: additional references included in the protocol amendment including; (Lan and Demets 1983), (Maude et al 2014)

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.

[redacted]

Protocol summary:

Protocol number	**CCTL019C2201**
Title	A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory DLBCL
Brief title	Study of efficacy and safety of CTL019 in adult DLBCL patients
Sponsor and Clinical Phase	Novartis Phase II Multicenter
Investigation type	Biological
Study type	Interventional
Purpose and rationale	DLBCL is the most frequent lymphoma subtype, representing 30-35% of all non-Hodgkin lymphomas (NHL). Two-thirds of patients are cured by a combination of chemotherapy agents ± radiotherapy in addition to rituximab, but one-third of patients have disease that is either refractory to initial therapy or relapses after standard therapy. Whether patients refractory to a rituximab-containing regimen should be retreated with rituximab is currently unknown based on available data. Relapsed and refractory patients have a poor prognosis, particularly those who do not respond to 2nd line chemotherapy. The median survival of patients non-responding to 2nd line chemotherapy is 4 months and only 4% are alive after 1 year. For patients relapsing with chemotherapy-sensitive disease, high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) provides the best chance of cure. However, due to advanced age and comorbidities, only half of all patients are eligible for such an intensive approach. Yet, only a modest minority of patients undergoing HSCT are cured. In summary, treatment options for patients who do not respond to 2nd line chemotherapy or who relapse after autologous HSCT are generally considered palliative. Novel therapies are urgently needed for this patient population. The B-cell marker CD19 has emerged as a target for DLBCL treatment in the past years. It is widely expressed on normal and malignant B-cells throughout B-cell maturation but not on pluripotent stem cells or non B-cell tissues. The vast majority of DLBCL expresses CD19. Autologous T cells have been developed that are genetically modified ex-vivo via a lentiviral transduction to express a chimeric antigen receptor (CAR) consisting of a CD19 antigen recognition domain attached to intracellular signaling domains that mediate T-cell activation. Data from patients with B-cell acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL), which are both CD19 expressing B cell malignancies, and preliminary data from patients with DLBCL show that CTL019 therapy has potent anti-tumor activity. The purpose of this study will be to determine the safety and efficacy of CTL019 in adults with relapsed or refractory DLBCL and to monitor all patients exposed to CTL019 for 5 years following CTL019 infusion.
Primary Objective(s) and Key Secondary Objective	To evaluate the efficacy of CTL019 therapy, defined as overall response rate (ORR), which includes complete response (CR) and partial response (PR) based on the [redacted] as determined by a central independent review committee. (Cheson et al 2014)
Secondary Objectives	• Evaluate safety of CTL019 • Evaluate time to response (TTR) • Evaluate duration of overall response (DOR) • Evaluate event free survival (EFS) • Evaluate progression free survival (PFS) • Evaluate overall survival (OS) • Evaluate safety and efficacy in histological and molecular subtypes • Characterize the in vivo cellular PK profile (levels, persistence, trafficking) of CTL019 transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid (CSF) and other tissues if available) • Describe the incidence of immunogenicity to CTL019 • Describe presence of RCL

[redacted]

Study design	This is a single arm, open-label, multi-center, phase II study to determine the efficacy and safety of CTL019 in patients ≥ 18 years with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The study will have the following sequential phases: Screening, Pre-Treatment, Treatment and Primary follow-up, Secondary follow-up, and Survival follow-up. The total duration of the study is 5 years. Efficacy will be assessed until progression; safety will be assessed throughout the full duration of the study. Patients will be monitored for delayed adverse events for up to 15 years after last CTL019 infusion in a separate destination protocol per the health authority guidelines. Approximately 100 patients will be enrolled to allow for 80 patients to be treated in the main study cohort. Further to this main cohort an additional cohort (Cohort A) will evaluate the impact of manufacturing site on clinical outcome. Approximately 18 patients will be enrolled in the additional cohort to allow for 15 patients to be treated. This cohort will assess the clinical profile (safety and efficacy, PK) of CTL019 manufactured at the Fraunhofer Institut für Zelltherapie (Leipzig, Germany). After the amendment 5 of the protocol, approximately 10 additional Japanese patients will be enrolled, to allow for at least 6 additional patients to be treated (total 9 treated in Japan). At the beginning of the trial, a safety run-in stage will be conducted to enroll at least three patients to assess the acute safety profile and product characteristics of the Novartis manufactured CTL019 cell product. The initial patients will be enrolled in this trial subsequently with minimum interval between CTL019 infusions of 14 days. Full safety profiles and product characteristics of these patents following lymphodepleting chemotherapy and CTL019 infusion will be reported to the Health Authorities.
Population	The target population is comprised of adults ≥ 18 years with relapsed or refractory DLBCL not eligible for HSCT. A minimum of 25 patients in each of the two most common molecular subtypes of DLBCL: GC and ABC type will be treated in the main cohort.
Inclusion criteria	1. Written informed consent must be obtained prior to any screening procedures 2. Patients must be ≥18 years of age 3. Histologically confirmed DLBCL (by central pathology review before enrollment). a. Sufficient FFPE tumor samples must be available for histological and molecular subtype testing along with a corresponding pathology report. A recent tumor sample obtained for the purpose of this study must be submitted however if not clinically feasible, an archival tumor biopsy from the most recent relapse may be submitted instead. Excisional biopsies should be submitted wherever possible; in cases where this is not possible, a core needle biopsy is allowable. Fine needle aspiration (FNA) is not allowed. 4. Relapsed or refractory disease after ≥2 lines of chemotherapy, including rituximab and anthracycline, and either having failed autologous HSCT, or being ineligible for or not consenting to autologous HSCT 5. Measurable disease at time of enrollment: a. Nodal lesions greater than 20 mm in the long axis, regardless of the length of the short axis b. Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) ≥ 10 mm in long AND short axis For detailed information please refer to Section 14.1 Appendix 1: Guidelines for efficacy evaluation in diffuse large B cell lymphoma and follicular lymphoma studies [redacted] 6. Life expectancy ≥12 weeks 7. ECOG performance status that is either 0 or 1 at screening 8. Adequate organ function: a. Renal function defined as: ● A serum creatinine of ≤1.5 x ULN OR ● eGFR ≥ 60 mL/min/1.73 m2 b. Liver function defined as: ● ALT ≤ 5 times the ULN for age

[redacted]

	● Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert–Meulengracht syndrome; patients with Gilbert-Meulengracht syndrome may be included if their total bilirubin is ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN c. Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation > 91% on room air d. Hemodynamically stable and LVEF ≥ 45% confirmed by echocardiogram or MUGA e. Adequate bone marrow reserve without transfusions defined as: ● Absolute neutrophil count (ANC) > 1.000/mm3 ● Absolute lymphocyte count (ALC) > 300/mm3, and absolute number of CD3+ T cells >150/mm3 ● Platelets ≥ 50.000//mm3 ● Hemoglobin > 8.0 g/dl 9. Must have an apheresis product of non-mobilized cells accepted for manufacturing 10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, and all male participants must use highly effective methods of contraception for at least 12 months following CTL019 infusion and until CAR T cells are no longer present by PCR. Highly effective contraception methods include: ● Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception ● Female sterilization (surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. ● Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient. ● BOTH of the following forms of contraception must be utilized: a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormonal vaginal ring or transdermal hormonal contraception AND b. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository ● Use of intrauterine devices (IUDs) is excluded due to increased risks of infection and bleeding Placed IUDs may remain in place but additional measures of contraception are mandated. Additionally, drugs that induce cytochrome P450 (CYP) enzymes can increase the clearance of sex hormones that are eluted by the devices and reduce contraceptive efficacy; given the poly-pharmacy for these patients this presents a real risk of device failure and possible resultant inadvertent conception. ● In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. 11. Sexually active males must use a condom during intercourse for 12 months 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 after treatment as they should not father a child in this period. A condom is required to be used also by vasectomized men (as well as during intercourse with a male partner or sterile female partner) as WBCs are a normal part of semen and transmission of CTL019 transduced cells may occur.

Exclusion criteria	1. Prior treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy 2. Treatment with any prior gene therapy product 3. Active CNS involvement by malignancy 4. Prior allogeneic HSCT 5. Eligible for and consenting to autologous HSCT 6. Chemotherapy other than lymphodepleting chemotherapy within 2 weeks of infusion 7. Investigational medicinal product within the last 30 days prior to screening Note: Investigational therapies must not be used at any time while on study until the first progression following CTL019 infusion 8. The following medications are excluded: ● Steroids: Therapeutic doses of steroids must be stopped > 72 hours prior to leukapheresis and > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: <12 mg/m2/day hydrocortisone or equivalent ● Immunosuppression: Any immunosuppressive medication must be stopped ≥ 2 weeks prior to leukapheresis and ≥ 2 weeks prior to CTL019 infusion. This could include check point inhibitors (monoclonal antibodies and small molecule modulators). ● Antiproliferative therapies other than lymphodepleting chemotherapy within 2 weeks of leukapheresis and 2 weeks prior to infusion ● Short acting drugs used to treat leukemia or lymphoma (e.g. tyrosine kinase inhibitors, and hydroxyurea) must be stopped > 72 hour prior to leukapheresis and > 72 hours prior to CTL019 infusion ● Other cytotoxic drugs, including low dose daily or weekly maintenance chemotherapy, must not be given within 2 weeks prior to leukapheresis and within 2 weeks prior to CTL019 infusion. ● Fludarabine may be associated with prolonged lymphopenia. This should be taken into consideration when evaluating the optimal timing for leukapheresis. ● Antibody use including anti-CD20 therapy within 4 weeks prior to infusion or 5 half-lives of the respective antibody, whichever is longer. Note: Rituximab is excluded within 4 weeks prior to infusion ● CNS disease prophylaxis must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate) 9. Prior radiation therapy within 2 weeks of infusion 10. Active replication of or prior infection with hepatitis B or active hepatitis C (HCV RNA positive) 11. HIV positive patients 12. Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion) 13. Unstable angina and/or myocardial infarction within 6 months prior to screening 14. Previous or concurrent malignancy with the following exceptions: ● Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry) ● In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study ● A primary malignancy which has been completely resected and in complete remission for ≥ 5 years 15. Pregnant or nursing (lactating) women 16. Intolerance to the excipients of the CTL019 cell product 17. Cardiac arrhythmia not controlled with medical management 18. Removed 19. Prior treatment with any adoptive T cell therapy

[redacted]

	20. Patients with T-cell rich/histiocyte rich large B-cell lymphoma (THRBCL), primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), EBV positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma 21. Patients with active neurological auto immune or inflammatory disorders (e.g. Guillain-Barre Syndrome, Amyotrophic Lateral Sclerosis)
Investigational and reference therapy	A single target dose of 5 x 10^8 of viable autologous CTL019 transduced T cells will be administered via intravenous infusion.
Efficacy assessments	Imaging (CT or MRI, PET-CT or dedicated PET), physical examination, bone marrow biopsy, B-Symptoms
Safety assessments	Adverse events and laboratory anomalies (type, frequency and severity) Selected adverse events Immunogenicity assessments (Humoral and cellular) Detection of replication competent lentivirus Detection of monoclonal or oligoclonal vector integration
PKs	Pharmacokinetic assessments planned for this trial include: • Characterization of CTL019 PK (e.g. Cmax, Tmax, AUCs, etc.) in blood, bone marrow and other relevant tissues if available by quantitative Polymerase Chain Reaction (qPCR) and/or flow cytometry. [redacted]
Data analysis	Primary endpoints: The primary analysis will be carried out after 80 treated patients have completed at least 3months of follow-up or have discontinued due to any reason. Selected efficacy and safety analysis will be updated annually. A final Clinical Study Report (CSR) will be produced once all patients complete or discontinue from the study. The primary efficacy endpoint, ORR will be analyzed based on the data observed by IRC in the full analysis set (FAS). The primary efficacy analysis will be performed by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that the ORR is greater than 20% at overall one-sided 2.5% level of significance, powered for ORR of 38%. The ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. The study will be considered successful if the lower bound of the 2-sided 95% exact confidence interval for ORR is greater than 20%, so that the null hypothesis that the ORR is less than or equal to 20% can be rejected. Sensitivity analyses will be performed on the Enrolled Set, the per-protocol set (PPS) and with all patients who satisfy all clinical eligibility criteria (excluding the inclusion criteria that pertains to the patient's accepted apheresis product) using the same method as described above. Additional sensitivity analysis will be performed using the ORR as assessed by local investigators in the FAS population. One interim analysis is planned when approximately 50 patients with DLBCL are treated and followed up for 3 months. If the lower bound of 99.08% exact confidence interval for ORR is greater than 20% then statistical significance can be declared. If the predicted probability of success (i.e., positive result at the end of the study) is less than 10% then the study may be terminated due to futility. Secondary endpoints: Analysis of secondary [redacted] endpoints will be descriptive and may include

[redacted]

	summary statistics such as means, standard deviations, 95% confidence intervals, if applicable, Kaplan-Meier curves and median time to event will be presented for time-to-event variables (DOR, TTR, EFS, PFS and OS), if appropriate. Pharmacokinetics parameters will be descriptively summarized and will include geometric and arithmetic means, SD, CV% and CV% geometric-mean, median, minimum, and maximum (for Tmax only median, minimum and maximum will be presented). PK parameters will be summarized by best overall response. Sample size: In two retrospective studies in relapsed and refractory DLBCL patients receiving 2nd or 3rd line therapies, the observed ORR were 14% and 20% (Seshadri et al 2008, Elstrom et al 2010). In a recent prospective clinical trial with ibrutinib in patients who had a median of 3 prior lines of therapy, the ORR in the ABC subtype (N=29) was 40% and in the GC subtype (n=20) 5% leading to an overall ORR of 21.7% (Wilson et al 2012). Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR>20%, 80 patients in the primary analysis will provide 94% power to demonstrate statistical significance at one sided 0.025 level of significance, if the underlying ORR is 38%. In this setting, an ORR of 24/80=30% will be needed to claim success. Assuming approximately 20% enrolled patients will not be infused due to reasons such as [redacted], worsening of patient's condition, etc., at least 100 patients need to be enrolled to ensure 80 patients are treated.
Key words	Relapsed/refractory DLBCL, CTL019

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Non-Hodgkin Lymphomas (NHL) comprise a heterogeneous group of malignancies. Estimated new cases are 70,800 and deaths are 18,990 in the United States (US) for 2014 (National Cancer Institute 2014). There were 66,371 lymphoid malignancies registered in 2000-2002 by 44 European cancer registries (Sant et al 2010). NHL are classified according to the current WHO classification (WHO 2008) into immature lymphoid neoplasms, mature B-cell neoplasms, T-cell and NK-cell neoplasms, and post-transplant lymphoproliferative disorders (PTLD). Mature B-cell lymphomas are further classified into indolent lymphomas (e.g. multiple myeloma, CLL) and aggressive lymphomas (e.g. diffuse large B-cell lymphoma (DLBCL). DLBCL is the most frequent lymphoma subtype, representing 30-35% of all non-Hodgkin lymphomas (NHL) (Ghielmini et al 2013). Estimated incidence in the European Union is 3–4/100 000/year, increasing with age from 0.3/100 000/year (35–39 years) to 26.6/100 000/year (80– 84 years) (Tilly H 2012). About 10,000 deaths per year are due to DLBCL in the US (National Cancer Institute).

Most patients with localized DLBCL can be cured with conventional combination immuno-chemotherapy or with combined–modality therapy. For patients with advanced-stage disease, the majority of patients can be cured with doxorubicin-based combination chemotherapy and rituximab (e.g. R-CHOP). Prognosis depends on individual risk factors. The International Prognostic Index (IPI) for aggressive NHL (diffuse large cell lymphoma) includes five significant risk factors prognostic of OS:

1. Patient age (≤60 years vs. >60 years)
2. Serum lactate dehydrogenase (LDH) (normal vs. elevated)
3. ECOG performance status (0 or 1 vs. 2–4)
4. Stage (stage I or stage II vs. stage III or stage IV)
5. Extranodal site involvement (0 or 1 vs. 2–4)

Patients with ≥2 risk factors after age-adjustment have a poor prognosis with a 5 year OS-rate of 21-46%. Age- and stage-adjusted modifications are used for younger patients with localized disease (Moller et al 2013). Very recently a revised IPI, the NCCN-IPI, has been proposed to better reflect the individual patient's risk in the rituximab era. Very similar to the original IPI, five prognostic factors were identified:

1. Patient age (>40 to ≤60 vs. >60 to ≤75 vs. >75 years)
2. Normalized serum LDH (>1 to ≤3 vs. >3 x ULN)
3. ECOG performance status (≥2)
4. Ann Arbor Stage (Stage ≥III)
5. Extranodal site involvement (Disease in bone marrow, CNS, liver/GI tract, or lung)

The NCCN-IPI can discriminate four prognostic groups: low (0-1), low-intermediate (2-3), high-intermediate (4-5), and high (6-8).

DLBCL is a heterogeneous disease with several molecular subtypes. Subtypes were identified by molecular profiling based on biologic similarity to normal stages of B-cell development,

[redacted]

dividing DLBCL into germinal center-like (GC), activated B-cell-like (ABC) tumors, and primary mediastinal large B cell lymphoma (PMBCL) (Lenz et al 2008) (Alizadeh et al 2000). The turnaround time for gene expression profiling (GEP) is not useful for initiation of therapy in most DLBCL patients. There are immunohistochemistry (IHC) algorithms, which approximate the GEP. These IHC models predict a 3-year overall survival (OS) of 85% in GC tumors compared to 65% in ABC tumors (Hans et al 2004).

Despite overall improvement in outcomes of DLBCL, approximately one-third of patients will develop relapsed/refractory (r/r) disease that remains a major cause of morbidity and mortality. Refractory disease is defined as a <50% decrease in lesion size with induction therapy or the appearance of new lesions (Cheson et al 2007). Progressive or relapsed disease reflects the appearance of new lesions after attainment of complete remission (CR) (Cheson et al 2007). Relapsed and refractory patients have a poor prognosis, particularly those who do not respond to 2nd line chemotherapy (Friedberg 2011). Left untreated, life expectancy is 3 to 4 months, similar to what is seen in patients not responding to 2nd line chemotherapy (Elstrom et al 2010). While approximately 60% of patients with r/r DLBCL remain sensitive to conventional 2nd-line salvage immunochemotherapy, <10% have prolonged disease-free survival. (Gisselbrecht et al 2010) Patients with r/r DLBCL responding to 2nd-line immunochemotherapy and undergoing subsequent high-dose chemotherapy and stem cell transplantation (HSCT) maintain their response over longer time (3-year PFS 39% in patients with HSCT vs. 14% for patients without HSCT) (Gisselbrecht et al 2010) (Sehn 2012). Patients relapsing within 12 months of rituximab-containing 1st-line therapy have a particularly poor prognosis even with HSCT (Gisselbrecht et al 2010). Without HSCT, chemotherapy provides only short-term disease control in r/r DLBCL. For transplant candidates who fail second line therapy or who relapse post-transplant, prognosis is grave. Molecular analysis of biopsies from the CORAL trial in 2nd line DLBCL (Gisselbrecht et al 2010) showed equal distribution of GC vs. non-GC DLBCL (Thieblemont et al 2011).

In summary, treatment options for patients who do not respond to 2nd line salvage therapy or who relapse after autologous HSCT are only palliative and overall survival (OS) is 3-4 months. Novel therapies are urgently needed for this patient population.

Ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase (BTK), a key component of B cell receptor (BCR) signaling has preferential activity in the ABC subtype. The survival of ABC but not GC DLBCL cell lines is sustained by "chronic active" B cell receptor (BCR) signaling. Gain-of-function mutations affecting the BCR subunit CD79B occur in 21% of ABC but only 5% of GC DLBCL tumors. An open-label Phase II study (NCT01325701) with ibrutinib in patients who had a median of 3 prior lines of therapy, reported an ORR in the ABC subtype (N=29) of 40% compared to 5% in the GC subtype (n=20) leading to an overall ORR of 21.7% (Wilson et al 2012). Rituximab, a chimeric monoclonal antibody against CD20, improves the survival of both the GC and non-GC subtypes analyzed by Hans algorithm (Fu et al 2008). Based on current experience, CTL019 is expected to be effective in the different molecular DLBCL subtypes.

1.1.1 Historical experience with retroviral gene therapies

To date, malignant cell transformation after vector-mediated insertional mutagenesis has been observed in three clinical entities (X-linked Severe Combined Immunodeficiency [SCID-X1], Chronic Granulomatous Disease [CGD], and Wiskott-Aldrich Syndrome [WAS]) which have

[redacted]

involved the use of first-generation gamma-retroviral vectors harboring long terminal repeats (LTRs) with strong enhancer/promoter sequences (Hacein-Bey-Abina et al 2003, Howe et al 2008, Boztug et al 2010, Stein et al 2010, Persons and Baum 2011). In contrast, data from 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).

Retroviral vectors are useful gene delivery vehicles because they insert a deoxyribonucleic acid (DNA) copy of their genome into the host cell. However, insertion of vector sequences is distributed throughout the cellular genome and insertion has the potential to up-regulate, dysregulate, or knockout local gene expression. Thus, there has always been a theoretical risk of insertional oncogenesis resulting from disruption of normal function of genes that control cell growth. This risk has been realized in a clinical trial utilizing murine-derived retroviral vectors to transfer the γ signaling chain to stem cells of infants with SCID-X1 (Hacein-Bey-Abina et al 2003). A total of 4 of 9 children in that trial have developed integration site-induced cancers, and one of those children died after relapse. In a parallel study where the same disease load and target cells were used, no tumorigenesis was observed at first, suggesting that minor differences, such as vector envelope and stem cell growth factors, might be relevant in long term safety of integrating vectors (Gaspar et al 2004). However, in December of 2007, one of the 10 children treated in that study also developed insertion-mediated oncogenesis (Howe et al 2008). Today, the causes of insertional oncogenesis remain poorly understood, but in the SCID-X1 studies, a common integration site, LMO-2, is observed in at least 3 of the 5 patients. In general, the target cell, vector, and disease payload are considered major factors contributing to the risks of vector-induced tumors. However, there is insufficient data to date to support the relative contribution of each of these factors in assuring safety of retroviral gene transfer.

Lentiviral vectors are a major subset of retroviral vectors, but demonstrate distinct integration patterns compared to oncoretroviral vectors which have been the predominant vector to date for gene transfer studies. The integration pattern of lentiviral vectors tends to be inside active transcription units as opposed to upstream in the locus control region where the insertion would have a greater chance of up-regulating gene expression. In addition, lentiviral vectors have no enhancer activity in their long terminal repeat (LTRs) regions and have lower levels of poly-A read-through, all factors which may improve gene transfer safety (Zaiss et al 2002). Thus, it may be that lentiviral vectors are a safer alternative to oncoretroviral vectors for gene transfer. Animal models have provided supporting evidence for this (Montini et al 2006). As lentiviral vectors are also superior for gene transfer, it is anticipated that these vectors will ultimately replace oncoretroviral vectors for stable gene transfer.

[redacted]

In direct contrast to oncoretroviral vectors, lentiviral vectors have not been shown to be oncogenic in nature except for a single study in neonatal mice where direct injection for liver delivery was performed (Themis et al 2005). The oncogenesis in this study may be associated with a vector element that can be modified to reduce such a risk (Schambach et al 2006), and also may be unique to the animal model used in that study. A newer study in tumor prone mice comparing the tumorigenicity of retroviral vectors to lentiviral vectors demonstrated that lentiviral vector gene transfer into hematopoietic stem cells of up to an average of 6 copies per cell was not tumorigenic in contrast to retroviral vectors at an average copy number of 3 per cell (Montini et al 2006). It is notable that T cell leukemia is not a recognized side effect of human immunodeficiency virus (HIV) lentiviral infection.

More recently, retroviral and lentiviral safety has been demonstrated in modified T cell gene therapy trials. A long-term retrospective study of >500 patient-years of collective patient samples tested for at least 11 years after infusion from three clinical trials using gamma-retroviral modified T cells to express CD4zeta chimeric antigen receptor (CAR) did not show evidence of transgene silencing, atypical gamma-retroviral integration patterns, or clonal expansion (Scholler et al 2012). A favorable safety profile was also determined for a conditionally replicating HIV-derived lentivirus that delivered HIV envelope antisense to patient T cells. In two separate treatment cohort analyses, no evidence for insertional mutagenesis or enrichment of vector copies near proto-oncogenes was observed (Levine et al 2006, and Wang et al 2009). These data represent follow-up after 21-36 months (Levine et al 2006) and 28-32 weeks (Wang et al 2009). Another group reported no apparent risk of vector related AEs following 263 infusions of autologous, lentiviral transduced T cells with a long ribonucleic acid (RNA) antisense to HIV-1 envelope (McGarrity et al 2013). More recently *ex vivo* lentiviral transduced hematopoietic stem cells were used to correct an inherited storage disease in three children and in an inherited WAS in 3 children with follow up for up to 24 months and 20-32 months, respectively. Lentiviral integration studies showed sustained gene marking with polyclonal engraftment of transduced cells with no evidence of aberrant clonal expansion, no evidence of *in vivo* selection of clones carrying integrations near oncogenes and therefore no evidence of vector-induced genotoxicity (Biffi et al 2013, Aiuti et al 2013).

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

1.2.1 Overview of CTL019

Immunotherapy is a treatment that involves activating or enhancing the immune system to help fight diseases including cancer. Adoptive immunotherapy with allogeneic donor leukocytes (e.g. donor lymphocyte infusion) has potent anti-leukemic effects, however the benefit is confined largely to patients with myeloid leukemia's, as B-ALL has a durable remission rate of less than 10% (Kolb et al 1995), and often at the cost of substantial morbidity due to GVHD (Appelbaum 2001, Sullivan et al 1989).

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.

[redacted]

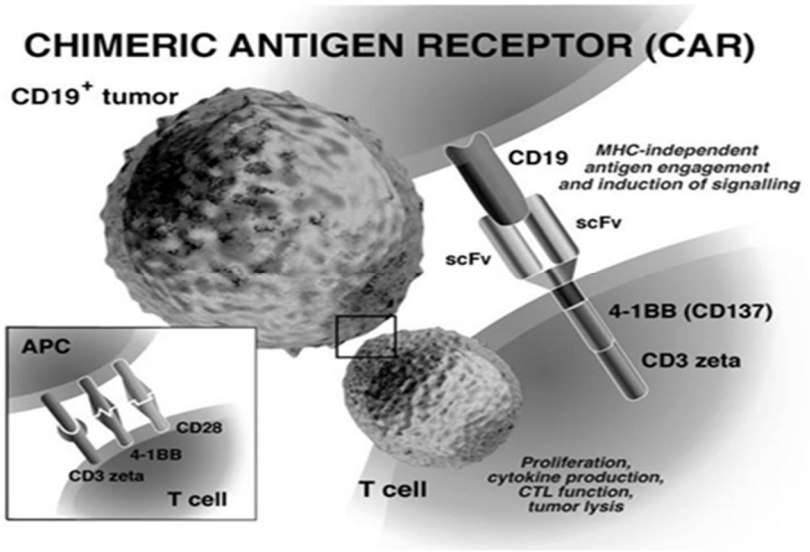
Unlike T cell receptors (TCR), CARs allow the T cells to specifically target and destroy tumor cells in a Major Histocompatibility Complex (MHC) independent manner (Mellman et al 2011).

A promising target antigen for B cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors (Sadelain et al 2003, Brentjens et al 2010, Porter et al 2011). CD19 is not expressed 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 (Ledbetter et al 1988, Stamenkovic and Seed 1988, Fearon and Carroll 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 (Ledbetter et al 1988, Stamenkovic and Seed 1988, Tedder and Isaacs 1989, Fearon and Carroll 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).

CTL019 (CART-19) 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 lymphocytes transfected with chimeric receptor genes to combine the effector functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner (Gross et al 1989, Pinthus et al 2003). These receptors have the ability to recognize intact membrane proteins independent of antigen processing. The tumor antigen binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the heavy chain variable domain (V_H) and light chain variable domain (V_L) joined by a peptide linker of about 15 residues in length (Mullaney et al 2001).

Figure 1-1 CTL019 chimeric antigen receptor design



Early results from ongoing clinical trials of CTL019 in r/r CLL and r/r ALL have shown promising and durable anti-tumor efficacy (Porter et al 2011, Grupp et al 2013, Maude et al 2014). It is anticipated that CTL019 may offer a therapeutic alternative for patients with r/r B cell malignancies, including DLBCL, who are either SCT ineligible or who have relapsed after SCT, which may offer a greater durability of remission than current salvage therapies. In the future CTL019 may also have the potential to replace SCT as a therapeutic choice, expanding patient eligibility by obviating the need for matched donors along with potentially lower rates of upfront mortality and morbidity. For further information refer to the [CTL019 Investigator's Brochure].

1.2.1.1 Non-clinical experience

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

1.2.1.2 Clinical experience

At the National Cancer Institute, 10 patients with NHL (4 DLBCL, 4 PMBCL, 2 low grade lymphomas) have received CAR modified CTLs directed against CD19. (Recombinant DNA Advisory Committee (RAC) meeting 2013). Response rate was 70% (DLBCL: 1 CR, 2 PR, 1 SD; PMBCL: 1 CR, 1 PR, 1 SD, 1 NE; Other: 2 PR). At the University of Pennsylvania (UPENN), a Phase II trial with CTL019 in 30 heavily pretreated, relapsed/refractory NHL patients including 9 with DLBCL has started in January 2014. To date fourteen patients (9 DLBCL, 5 FL) have been treated with CTL019. Most patients had early clinical responses, with 2 out of 2 patients evaluated with CT showing PET-negative CRs. One patient progressed before response assessment. In ALL, across both children and adults, more than 85% of patients have achieved a complete response (CR) within 28 days of infusion (Grupp SA 2013, unpublished data as of February 19th, 2014). In CLL, the response rate has been lower, and no relapses have yet been observed in patients who achieve CR (Porter DL 2013, unpublished data as of February 19th, 2014).In patients with severe CRS, tocilizumab was administered with rapid (within hours) resolution of fevers and hemodynamic instability. Patients achieving a complete remission (CR) also experienced B-cell aplasia and hypogammaglobulinemia, which was supported with periodic intravenous immune globulin infusions (Grupp et al 2013). For further information refer to the [CTL019 Investigator's Brochure].

[redacted]

There are currently 5 ongoing human treatment studies using CTL019 therapy (Table 1-1). Results from these ongoing clinical trials of CTL019 in r/r CLL and r/r adult and pediatric ALL have shown promising and durable anti-tumor efficacy (Porter et al 2011, Grupp et al 2013, Maude et al 2014). It is anticipated that CTL019 may offer a therapeutic alternative for patients with r/r B cell malignancies who are either SCT ineligible or who have relapsed after SCT, which may offer a greater durability of remission than current salvage therapies. In the future, CTL019 may also have the potential to replace allogeneic SCT as a therapeutic choice, expanding patient eligibility by obviating the need for matched donors along with potentially lower rates of upfront mortality and morbidity.

As of January 2015, 26 patients (18 DLBCL, 8 FL) have been enrolled in the University of Pennsylvania (UP) phase II trial (UPCC13413), and 20 patients have been treated with CTL019 ($5x10^8$ CTL19+ cells). Overall response rate (ORR) at three months after CTL019 infusion in 18 evaluable patients (12 DLBCL, 6 FL) was 67%, with 6 patients showing PET-negative CRs (5 DLBCL, 1 FL), and 6 patients showing disease progression. Six patients progressed before response assessment. Although data is preliminary in terms of duration of response, all responding patients so far remain in remission up to 280 days. (Schuster et al. ASH 2014, abstract 3087). Other investigators have also reported their results in CLL, NHL and ALL with autologous anti-CD19 CARs (Davila et al 2014, Brentjens et al 2011, Kochenderfer et al 2012).

To date, no vector related AEs have been seen with higher CTL019 transgene levels of expression or persistence, with the longest periods of observation being 9, 10, and 22 months in three pediatric patients with r/r ALL and 12, 22, 42 and 43 months in 4 adult patients with r/r CLL as of March 2014.

Post-infusion monitoring for RCL in these trials with University of Pennsylvania manufactured CTL019 (CART-19) therapy has shown no Vesicular Stomatitis Virus, Glycoprotein (VSV-G) by quantitative Polymerase Chain Reaction (q-PCR) (test for RCL) detectable in any of the patient samples at time points up to 2 years (7 patients from UPCC03712 trial; 16 patients form UPCC04409 trial, 11 patients from CHP959 trial).

Clinical Cellular Kinetics (Pharmacokinetics)

r/r ALL

Based on preliminary data, following infusion of CTL019, a rapid expansion occurs with a median Tmax occurring around 9-10 days as measured by qPCR (copies of CTL019 transgene) and flow cytometry (% of CD3+/CTL019+ and % CD3/CD8+ CTL019) in patients with a best response of CR or CRi. The mean half-life in the CR/CRi patients (n=35) were reported to be approximately 32 days measured by PCR. The mean overall exposure (AUC28d) was approximately 12.4 and 15.5-fold lower in NR patients (n=3) compared with CR/CRi (n=46) for % of CD3+/CTL019+ and % CD3/CD8+ CTL019, respectively, signifying the roles of both expansion and persistence for eliciting clinical response. AUC84d and Cmax also tended to be higher for CR/CRi patients compared to NR as measured by both qPCR and flow cytometry. Bone marrow concentrations of CTL019 (quantified as CD3+/CTL019+%) were measurable at 1 month post-CTL019 infusion in 40 of 46 CR/CRi pediatric ALL patients, and within those patients by 3 months measurable in 24 of 46 patients sampled showing trafficking of CTL019 to the bone marrow space as measured by flow cytometry. Bone marrow data was limited in

[redacted]

NR patients (n=2) with very low levels by 1 month. Trafficking of CTL019 cells has also been demonstrated into the cerebral spinal fluid (CSF) in this patient population (Grupp 2013).

CLL

Rapid expansion occurs with a median Tmax occurring around 13 days post infusion in CLL patients with a best response of CR or CRi as measured by qPCR (copies of CTL019 transgene) and flow cytometry (% of CD3+/CTL019+ and % CD3/CD8+ CTL019). Limited data from preliminary analysis suggests that Tmax may be slightly delayed (ranges from 17.0 -28.0 days) in CLL patients achieving a PR/ PRi/NR/PD in Study A2201 relative to CR/CRi patients. Based on limited data there appears to be a trend for a longer CTL019 half-life in CR/CRi CLL patients compared with PRi and PRi/NR/PD patients, this trend is consistent with results observed in other indications (e.g. ALL).

[redacted]

Clinical Safety

Adult r/r ALL

As of January 2015, 18 adult r/r ALL patients have been treated on a phase I trial (UPCC04409 protocol, NCT01029366) or phase II trial (UPCC21413 protocol, NCT02030847) under the Penn IND. The age range is 21 to 66 years. CRS was seen in 16 of 18 patients. Twelve patients (66.7%) had grade 3 or 4 CRS and nine (75%) of these patients required anti-cytokine therapy with tocilizumab.

The phase II adult r/r ALL UPCC21413 trial utilized a single infusion of a higher dose of CTL019 cells. Among the first six patients treated, three deaths were attributable to Grade 5 refractory CRS in the setting of significant concomitant infections. The subsequent six patients on this trial were then treated with a reduced cell dose of CTL019. Two early deaths out of these six subsequent patients were seen with the lower dose of CTL019 cells, however, CRS in these two cases was deemed not to be refractory to intervention.

Adult r/r B-NHL

At the University of Pennsylvania (UP), a Phase II trial with CTL019 in heavily pretreated, relapsed/refractory NHL patients has started in January 2014 (UPCC13413). This trial includes adult patients with relapsed or refractory NHL including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL). As of January 2015, 26 patients (18 DLBCL, 8 FL) have been enrolled, and 20 patients have been treated with CTL019 ($5x10^8$ CTL19+ cells). All patients developed fever following T cell infusion, attributed to cytokine release syndrome (CRS). CRS was detected in 15 patients: 13 patients with grade 2 CRS, 1 patient with grade 3, and 1 patient with grade 4 CRS. One patient received steroids and tocilizumab for grade 4 CRS. CRS occurred within the first week of T cell infusion in all patients. Neurologic toxicity was observed in 11 pts (1 grade 3 encephalopathy that

[redacted]

resolved with corticosteroids; 1 grade 3 dysarthria and grade 3 ataxia). There was no treatment-related mortality (Schuster et al. ASH 2014, abstract 3087).

Other institutions have also reported fatal SAEs in adult patients associated with the use of CD19 CARs. In one of these fatal SAEs, death occurred 44 hours post-CD19 CAR T cell infusion. The investigators concluded that concomitant sepsis was the most likely cause of death and attributed the etiology of the death as possibly related to CAR T cell infusion (Brentjens 2010). Two other fatal SAEs in adult patients have been reported by other institutions outside the University of Pennsylvania. Each of these deaths occurred within the first two weeks of CAR infusion.

Table 1-1 Summary of ongoing human studies as of January 2015

Study	Patients infused	Population	Infusion Schedule	Median CTL019 transduced cells
UPCC04409, Phase I	20 (14 CLL and 6 ALL)	r/r CD19+ adult leukemia/lymphoma	Day 0; 10% Day 1; 30% Day 2; 60%	1.4×10^8
CHP959, Phase I	43 (42 ALL)	r/r CD19+ pediatric leukemia/lymphoma	Day 0; 10% Day 14; 30% Day 28; 60% Later amended to Day 0, 1 and optional Day 14 (or later)	3.5×10^6/kg body weight
UPCC03712, Phase II	28	r/r CLL	Day 0; 100%	Low dose cohort (14): 2.1×10^7 High dose cohort (14): 2.6×10^8
UPCC21413, Phase II	12	r/r ALL	Day 0; 100%	5×10^7
UPCC13413, Phase II	26 enrolled (18 DLBCL and 8 FL)	NHL: Follicular (FL), Mantle Cell (MCL) & Diffuse Large B-Cell (DLBCL)	Day 0; 100%	5×10^8
14BT022, Phase II	15	r/r ALL	Day 0; 100 %	5.0 x 106/kg body weight

For further information regarding clinical experience with CTL019, refer to the [CTL019 Investigator's Brochure]

2 Rationale

2.1 Study rationale and purpose

Current therapies for DLBCL consist of combination chemotherapies with CD20-targeting immunotherapies. While over 50% of patients reach long-lasting complete remissions, approximately one-third of patients are refractory to therapy or will relapse after initial response. These patients have a poor prognosis, especially if they do not respond to or are not eligible for salvage regimen including HSCT.

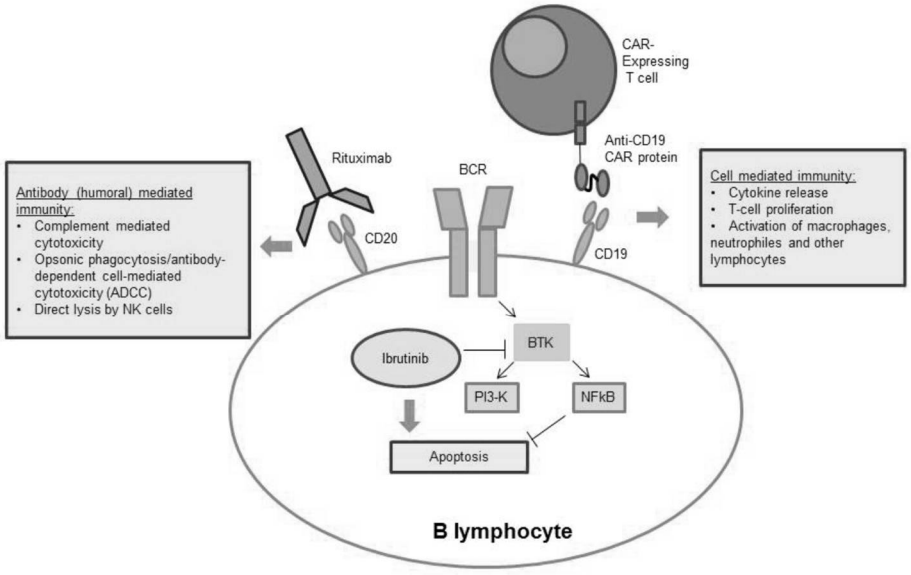
The B-cell marker CD19 has emerged as a target for DLBCL treatment in the past years. It is widely expressed on normal and malignant B-cells throughout B-cell maturation but not on pluripotent stem cells or non–B-cell tissues. The vast majority of DLBCL expresses CD19

(Kimura et al 2007). We have developed chimeric antigen receptor (CAR) T cells to target CD19+ cells (CTL019). This approach involves autologous patient-derived T cells that are genetically modified *ex-vivo* via lentiviral transduction to express a CD19 antigen recognition domain attached to intracellular signaling domains that mediate T-cell activation. Data from patients with B-cell acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and other CD19 expressing B cell lymphomas show that CTL019 therapy has potent anti-tumor activity.

As of January 2015, 26 patients (18 DLBCL, 8 FL) have been enrolled in the University of Pennsylvania (UP) phase II trial (UPCC13413), and 20 patients have been treated with CTL019 ($5x10^8$ CTL019+ cells). Overall response rate (ORR) at three months after CTL019 infusion in 18 evaluable patients (12 DLBCL, 6 FL) was 67%, with 6 patients showing PET-negative CRs (5 DLBCL, 1 FL), and 6 patients showing disease progression. Six patients progressed before response assessment. Although data is preliminary in terms of duration of response, all responding patients so far remain in remission up to 280 days. (Schuster et al. ASH 2014, abstract 3087).

If CTL019 has preferential activity in a subtype of DLBCL is currently unknown. Since the mechanism of action of CTL019 is independent of BCR signaling, it is anticipated that patients with GC and ABC subtype and patients failing ibrutinib will equally respond to CTL019. In addition, a cross-resistance with CD20-targeted therapies such as rituximab is not expected.

Figure 2-1 Mechanisms of actions of rituximab, ibrutinib and CTL019 in B lymphocytes:



Adapted from Taylor RP 2007, Knochenderfer JN 2013, Novero A 2014

The monoclonal antibody rituximab targets CD20 on the cell surface, activates complement mediated cytotoxicity, opsonic phagocytosis also known as antibody-dependent cell-mediated cytotoxicity (ADCC) and direct lysis by NK cells. Ibrutinib targets the intracellular Bruton's tyrosine kinase and interferes with cell signaling, inhibits the activating signal for PI3K and for NFkB, an inhibitor of apoptosis. CTL019, CAR modified T-cells targeting CD19, lead to cytokine release, T-cell proliferation

[redacted]

and activation of macrophages, neutrophils and other lymphocytes. Preclinical models are being investigated to determine the effects of ibrutinib on CTL019.

In summary, novel therapies for relapsed or refractory DLBCL are urgently needed. Targeting CD19 by CAR expressing T-cell therapy has been shown to be effective eliminating very advanced B-cell malignancies and has the potential to induce complete remissions in patients otherwise beyond treatment. This trial will therefore assess the clinical activity of CTL019 in patients with relapsed/refractory DLBCL measured as overall response rate.

2.2 Rationale for the study design

This is a 5 year single arm, multi-center, phase II study to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory DLBCL. A single arm therapy study design is supported by the absence of effective therapies in this setting, and high unmet medical need. This study will enroll approximately 100 patients to allow 80 patients treated in the main cohort. Approximately 18 patients will be enrolled in cohort A to allow for 15 patients to be treated. After the amendment 5 of the protocol, approximately 10 additional Japanese patients will be enrolled, to allow for at least 6 additional patients to be treated (total 9 treated in Japan). After assessment of eligibility, patients qualifying for the study will be enrolled and start lymphodepleting chemotherapy, i.e. fludarabine and cyclophosphamide, or bendamustine for patients with cyclophosphamide resistance, as indicated per protocol, followed by a single dose of CTL019 transduced cells.

Previous clinical data with CTL019 therapy has been generated using cell product manufactured at the Cell and Vaccine Production Facility (CVPF) at the University of Pennsylvania. This trial will utilize product manufactured at a Novartis manufacturing facility. A limited **safety run-in stage** will be conducted at the beginning of this trial. These patients will be included in the total targeted patient population.

The efficacy of CTL019 will be evaluated through the primary endpoint of ORR as determined by an Independent Review Committee (IRC) assessment, including CR and PR, until progression or relapse for up to 5 years. The choice of ORR as the primary endpoint is based on evidence that ORR is a standard outcome measurement in DLBCL (Cheson et al 2007). Objective response is the most predictive factor of outcome after autologous HSCT (i.e. after salvage therapy) (Johnston et al 2008). For patients not responding to the first salvage regimen, the outcome is extremely poor, with a median OS of approximately 4 months (Elstrom et al 2010, Friedberg 2011).

Safety will be monitored throughout the trial. Per Health Authority guidelines (FDA, EMA) for gene therapy products or advanced therapy medicinal products that utilize integrating vectors (e.g. lentiviral vectors), all patients treated with CTL019 must be monitored for specific toxicities for up to a total of fifteen years, irrespective of their response to CTL019. All patients will be monitored in this trial for five years, followed by semiannual and annual safety assessments in a separate long-term safety follow-up protocol (CCTL019A2205B) for additional ten years. The purpose of this is to assess the risk of acute and delayed AEs suspected to be related to CTL019 therapy, and to monitor for replication competent lentivirus (RCL).

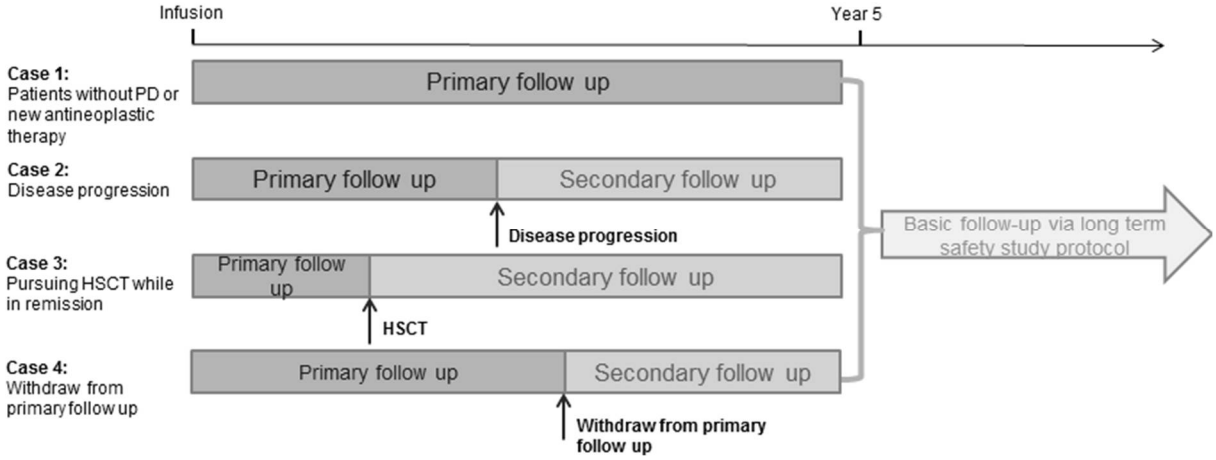
During the “treatment and primary follow-up phase” all adverse events will be collected for the first 12 months only. After 12 months, if a patient is still in the primary follow-up phase, only

[redacted]

protocol defined adverse events and adverse events of special interest will be collected. Patients completing or discontinuing from this primary follow-up phase will have an "End of Treatment and Primary Follow-Up Visit". Patients who discontinue the "treatment and primary follow-up phase" before month 60 will continue to be followed in the secondary follow-up phase in order to collect data on delayed adverse events, in line with HA recommendation for gene therapy products. Patients not entering or finishing the secondary follow-up will be followed in a separate long-term safety follow-up protocol (LTFU, CCTL019A2205B). It is anticipated that patients may leave the primary follow-up and move to secondary follow-up for the following reasons (Figure 2-2):

1. Progression of disease/relapse
2. Pursuing HSCT while in remission
3. Withdrawal from the primary follow up

Figure 2-2 Expected flow of patients in CTL019C2201



Based on current clinical experience with CTL019 therapy acute toxicities are expected in the first 28 days after single infusion of CTL019 cells. Expected acute toxicities include elimination of normal CD19 positive B cells, cytokine release syndrome (CRS)/macrophage activation syndrome (MAS) associated with the onset of antitumor responses mediated by large numbers of activated T cells, tumor lysis syndrome (TLS), and toxicities associated with the lymphodepleting chemotherapy conditioning regimen used with adoptive T-cell therapy. For more details and guidance on management of these toxicities refer to Section 6.2.4.2.1. These acute toxicities, with the exception of B cell depletion or aplasia, are all typically reversible and resolved within several weeks to months of CTL019 infusion.

Potential long-term toxicities of CTL019 therapy may include continued B cell aplasia with increased risk of infections if CTL019 cells persist. Other potential toxicities may include insertional site oncogenesis, expression of replication competent lentivirus (RCL) detection, and potential effects of maternal CTL019 cells on pregnancy outcome. RCL, autonomous proliferation of infused CTL019 T cells, and insertional site oncogenesis during the CTL019 therapy trials have not been observed to date.

Collection of such long term effects of CTL019 cell therapy will help to further define the risk-benefit profile of CTL019 in patients with B cell malignancies. These observations will also

[redacted]

serve to provide further guidance to patients, health care providers and investigators of such risks and their detection and management.

Patients that complete or discontinue from this study will be requested to consent to the LTFU study, CCTL019A2205B, to meet health authority guidelines.

2.2.1 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation (Dummer et al 2002), a recent finding that naive T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naive T cells are reduced below a certain threshold (Goldrath and Bevan 1999, Surh and Sprent 2000). Host lymphodepletion may enhance the effectiveness of adoptively transferred T cells (Dummer et al 2002). Homeostatic T cell proliferation can lead to activation of certain immune cell subsets (King et al 2004), providing a clue to improved anti-tumor responses. T cells can undergo up to seven rounds of cell division after being deprived of contact with antigen presenting cells (Kaech and Ahmed 2001, van Stipdonk et al 2001). Lymphodepletion eliminates regulatory T-cells and other competing elements of the immune system that act as "cytokine sinks", enhancing the availability of cytokines such as IL-7 and IL-15 (Klebanoff et al 2005). This hypothesis has been tested clinically in patients with metastatic melanoma refractory to conventional treatments (Dudley et al 2002). The patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide (60 mg/kg x 2 days) and fludarabine (25 mg/m^2 x 5 days) prior to adoptive transfer of T cells. More than 40 patients with myeloma have been treated with CARs and lymphopenia after lymphodepleting chemotherapy, and observed improved engraftment (Laport et al 2003, Rapoport et al 2005). In this protocol, it is proposed to infuse CTL019 T cells into patients that are rendered lymphopenic as a result of cytotoxic chemotherapy. Recent data indicates that the increased antitumor efficacy of adoptive transfer following host conditioning is more than simply "making room" because the quantitative recovery of adoptively transferred T cells in mice reveals that *in vivo* proliferation following adoptive transfer is identical in mice with or without previous irradiation (Palmer et al 2004).

As of January 2015 in the ongoing CTL019 lymphoma study UPCC13413, all 20 patients infused with CTL019 cells received a lymphodepleting chemotherapy prior to adoptive transfer of T cells. Five patients received a lymphodepleting regimen consisting of bendamustine, nine patients received cyclophosphamide, one patient received fludarabine and cyclophosphamide, two patients received EPOCH; one patient received lenalidomide + CHOP, and two patients received cyclophosphamide in combination with radiation therapy (Schuster et al. ASH 2014, abstract 3087). Similarly, in ongoing CTL019 pediatric and adult ALL studies, most patients infused with CTL019 received a lymphodepleting conditioning regimen prior to adoptive transfer of T cells.

For further information regarding clinical experience with lymphodepletion prior to CTL019 infusion, refer to the [CTL019 Investigator's Brochure].

2.3 Rationale for dose and regimen selection

The dose selected for this trial is a single infusion of 5 x 10^8 CTL019 cells based on available data collected in patients with CLL, ALL and non-Hodgkin's lymphoma (NHL) indicating it is well tolerated. A clear relationship between response and dose of infused transduced CTL019

[redacted]

cells has not been established in data collected to date in patients with CLL, ALL, and non-Hodgkin's lymphoma but will be explored further in this trial. This is likely the consequence of the ability of CTL019 transduced cells to proliferate and expand extensively (e.g. 1000 to >10,000 fold) *in vivo*. Thus, the administered dose may underestimate the number of CTL019 cells *in vivo* following engraftment and expansion and will vary from patient to patient, and across diseases. Additional considerations in this dose selection will have to take into account the manufacturing feasibility of producing adequate numbers of CTL019 transduced cells and important differences in toxicity profile across indications.

Animal studies supported a threshold dose of CTL019 cells and therefore the initial clinical dose selection was within the range of 1 x 10^7 to 1 x10^9 CTL019 transduced cells (Milone et al 2009). Please see IB for further information on preclinical studies.

For safety reasons, initial dosing in the pilot study CTL019B2102J/UPCC04409 was divided among three split infusions: 10%, 30% and 60% of the total cell dose (up to 5x10^9). In this study, autologous CART-19 transduced cells were administered to 20 patients with relapsed/refractory CD19+ B-cell malignancies (14 CLL and 6 ALL). While the target cell dose was 5x10^9, the acceptable range was 1.5 x10^7 to 5 x10^9 CART-19 cells. Of the 11 patients that had a CR, 7 patients received a single infusion (approximately 5x10^8 cells) due to the onset of fevers, yet CRs were observed with either 1 to 3 infusions. Thus, patients responded both after a single infusion and after multiple infusions of CART-19 cells.

Based on results from study CTL019B2102J/UPCC04409, the target dose levels of 1-5x10^7 and 1-5x10^8 CART-19 transduced cells were selected for a subsequent dose optimization study in CLL (study CTLA019A2201/UPCC03712). Patients with heavily pretreated CLL frequently have a significantly lower percentage of CD3+ cells in leukapheresis products than patients with other types of hematologic malignancy. Lentiviral transduction and expansion therefore could be limited in the setting of reduced CD3+ cells. As observed in the phase I study, manufacturing success rates declined to approximately 50% when targeting 10^9 or more CART-19 cells. Targeting 10^8 or fewer cells has not been an issue from a manufacturing standpoint. A single infusion of CART-19 cells in the dose optimization study (CTL019A2201/UPCC03712) was clinically well tolerated and responses have been seen with both dosing schemas. The most recent data update from this dose optimization study in CLL have not shown a discernible difference with regards to incidence or severity of CRS or any other toxicity between the low and the high dose schedules tested (i.e. 1-5x10^7 vs 1-5x10^8). Of the 26 patients dosed to date, 14 have experienced CRS (6 in the high dose and 8 in the low dose arm, respectively). CRS cases have occurred several days post CTL019 infusion and have been generally mild to moderate and manageable. No treatment related deaths have been noted in either arm. Notably, in patients with CLL achieving CR or a lasting PR, the number of infused CTL019 transduced cells has ranged from 1.4 x 10^7 to 1.1 x 10^9 cells. This two-log-fold difference did not support a statistically significant dose response relationship in spite of a numerically higher response rate amongst patients dosed in the high dose arm. Thus far, 8 out of 23 assessable patients have responded (4 CR and 4 PR), including 5 (50%) responders in the high dose arm and 3 (23%) responders in the low dose arm (p=0.37).

In the ongoing trial UPCC13413 in adult patients with relapsed or refractory NHL (including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL)), treated patients have received a single dose of 5 x 10^8 CTL019 transduced cells

[redacted]

(translating into a median dose of 5.8 x 10^6/ kg (range: 3.7 – 8.9 x 10^6) CTL019 transduced cells).

Unique adverse events following T cell infusion included cytokine release syndrome (CRS) and neurologic disturbances. CRS occurred within the first week of T cell infusion, and there were no episodes of delayed CRS. Neurologic toxicity was observed in 11 pts: Three patients developed transient delirium (1 grade 2, 2 grade 3) and one patient developed a possibly related, grade 5 encephalopathy. Like in CLL, preliminary data suggest no dose-response or dose-toxicity relationship became obvious (18 evaluated patients January 2015).

Data from the adult ALL trials previously supported a safe and efficacious dose range of 1.4 x 10^7 to 1.1 x 10^9 CTL019 transduced cells. However, 3 patients with adult r/r ALL in study UPCC21413 died within 16 days post-CTL019 infusion possibly related to CTL019 infusion (in the presence of concomitant infectious complications in all three instances). After health authority consultation, the dose for treatment of patients with adult ALL in study UPCC21413 was reduced to 1 to 5 x 10^7 transduced CAR T cells. No deaths have occurred in ongoing pediatric ALL trials. In pediatric ALL patients, clinical responses were seen after the infusion of CTL019 transduced cell doses ranging from 1.1 to 18.1 x 10^6 transduced CTL019 cells/kg body weight with an age range of 5 to 22 and a weight range of 18.3 to 122.0 kg. Toxicity as assessed by severity of CRS appears to correlate with pre-infusion tumor burden in pediatric ALL but not with transduced CTL019 cell numbers within the range of cell doses studied. Therefore, the targeted CTL019 cell dose for pediatric ALL patients is 2 to 5 x 10^6 CTL019 transduced cells per kg body weight with a maximum dose of 2.5 x 10^8 CTL019 transduced cells (non-weight adjusted). Based on the current safety profile, no dose modifications were instituted in other indications than ALL.

It is important to note that the severity and incidence of CRS induced by similar CTL019 dosing schemas differs between adult ALL and CLL or NHL and therefore, dose selection for the latter indications should be based on toxicity and efficacy data observed in trials for patients with CLL or NHL. It is important to note that no deaths have been reported to date amongst more than 50 patients with CLL or NHL treated in clinical trials at the University of Pennsylvania. This is likely because the use of doses ranging from 1 to 5x10^8 cells in CLL or NHL (the dose range used to treat approximately two thirds of patients) has been associated with less frequent and more attenuated forms of CRS compared with those induced by the same dose range in adult ALL. Furthermore, in the dose optimization study in CLL, the highest dose range tested (1 to 5x10^8) renders numerically higher response rates compared with the lower dose range (1 to 5x10^7).

In summary, based on clinical experience from past and ongoing trials in r/r CLL and NHL at the University of Pennsylvania, where the upper range of the target dosing tested in study CTL019A2201/UPCC03712 (i.e. 1-5x10^8) was effective and safe, a target dose of 5 x 10^8 CTL019 viable transduced cells has been chosen for further development in CLL and NHL. The allowable dose range is 1-5x10^8 viable transduced cells.

2.4 Rationale for choice of combination drugs

Not applicable.

[redacted]

2.5 Rationale for choice of comparators drugs

Not applicable.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary: Evaluate the efficacy of CTL019 therapy in the main cohort	Overall response rate (ORR), which includes complete response (CR) and partial response (PR) as determined by IRC assessment in the full analysis set (FAS) of the main cohort In addition sensitivity analyses will be performed using the local investigator response assessments	Refer to Section 10.4
Key secondary: Not applicable	Not applicable	Refer to Section 10.5.1
Other secondary: Evaluate safety of CTL019	Type, frequency and severity of adverse events and laboratory abnormalities	Refer to Section 10.5.2
Evaluate time to response	Time to response, i.e. time between date of CTL019 infusion until first documented response (CR or PR)	
Evaluate duration of overall response (DOR)	Duration of response, i.e. the time from achievement of CR or PR, whichever occurs first, to relapse or death due to DLBCL	
Evaluate event free survival (EFS)	EFS, i.e. the time from date of CTL019 infusion to the date of first documented disease progression or relapse, new treatment for lymphoma or death due to any cause	
Evaluate progression free survival (PFS)	PFS, i.e. the time from date of CTL019 infusion to the date of first documented disease progression or death due to any cause	
Evaluate overall survival (OS)	OS, i.e., the time from date of CTL019 infusion to the date of death due to any cause	
Evaluate efficacy and safety in histological and molecular subgroups (GC, ABC, other)	ORR, PFS, OS, EFS, DOR and AEs in histological and molecular subtypes	
Characterize the *in vivo* cellular PK profile (levels, expansion, persistence) of CTL019 transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid and other tissues if available), summarized by clinical response	- PK parameters: Cmax, Tmax, AUCs, T1/2, Clast, Tlast and/or other relevant PK parameters in peripheral blood, bone marrow, as appropriate	
Characterize immunogenicity (pre-existing (pre-dose) and post-infusion) in patient treated with CTL019	-Summary of immunogenicity(cellular and humoral)	

[redacted]

Objective	Endpoint	Analysis
Describe presence of RCL	- RCL by VSV-g q-PCR	
Evaluate efficacy and safety in cohort A	ORR, PFS, OS, EFS, DOR and AEs in cohort A	
Evaluate the Overall response rate for all patients treated	ORR in all patients treated	

[redacted]

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This is a single arm, multi-center, phase II study to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory DLBCL. The study will have the following sequential phases for all patients: Screening (Section 7.1.1), Pre-treatment, Treatment and Primary follow-up, Secondary follow-up, and Survival follow-up.

Efficacy for all patients will be evaluated using CT/MRI based on the Lugano Classification (updated Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma; Cheson et al 2014; Barrington et al 2014) [redacted] If local health authorities require the use of specific imaging modalities (e.g., MRI) and/or a different imaging schedule for disease response assessment purposes a decision will be made on a case by case basis upon discussion between Novartis and the Investigator. Efficacy will be assessed at Day 28 and months 3, 6, 9, 12, 18, 24 months and then every 12 months for 5 years until documented disease relapse or disease progression. PET-CT will be performed at baseline and at Month 3. Due to the mechanism of action of CTL019, the Day 28 assessment should be interpreted in context of other clinical parameters that suggest true progression rather than pseudo-progression due to inflammatory changes and tumor swelling (De Velasco et al 2015).

. Although clinical guidelines (ESMO and NCCN) do not recommend routine imaging in patients in CR for longer than 2 years, in the context of this clinical trial an extended efficacy follow up by CT/MRI is justified.

At the beginning of the trial, a safety run-in stage will be conducted to enroll at least three patients to assess the acute safety profile and product characteristics of the Novartis manufactured CTL019 cell product. The initial patients will be enrolled in this trial subsequently with minimum interval between CTL019 infusions of 14 days. Full safety profiles and product characteristics of these patients following lymphodepleting chemotherapy and CTL019 infusion will be reported to the Health Authorities. The acute and subacute toxicity profile for CTL019 cell product manufactured at the University of Pennsylvania has been established in patients with r/r B-NHL with only low grade CRS observed in patients with DLBCL.

The data to be reported will include demographics, lymphodepleting chemotherapy, total and CTL019 transduced viable T cell doses, AE/ Serious Adverse Events (SAEs), standard laboratory data (hematology and chemistry) and CTL019 cellular PK.

For the purpose of safety onboarding of new sites, after the above safety run-in stage has been completed, a staggered approach will also be utilized at each new respective site (with no prior experience administering CTL019) and will occur as follows:

- 1st patient infusion, wait 14 days
- 2nd patient infusion, wait 14 days
- Following completion of this staggered enrollment of the first two patients, the new site may then proceed with infusion of patients without staggering the patients.

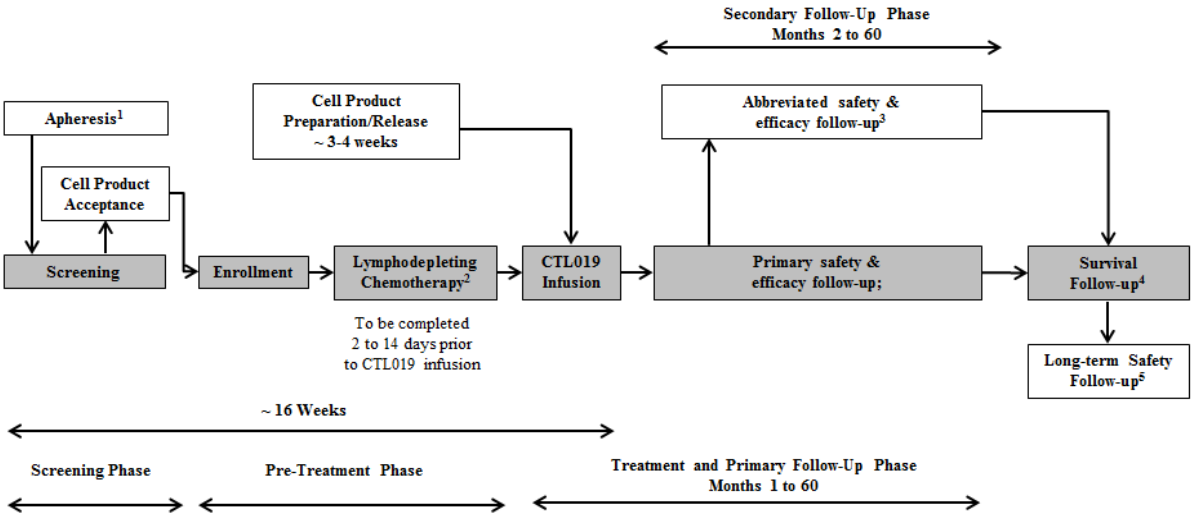
[redacted]

Safety will be assessed throughout the study.

One additional cohort has been added to the original main study cohort (80 patients treated with CTL019 manufactured at the Novartis manufacturing facility in Morris Plains, USA).

The additional cohort A will enroll approximately 18 patients to allow at least 15 patients infused with CTL019 manufactured at the Fraunhofer Institut für Zelltherapie. After the amendment 5 of the protocol, approximately 10 additional Japanese patients will be enrolled, to allow for at least 6 additional patients to be treated (total 9 treated in Japan).

Figure 4-1 CTL019C2201 study design



1 Performed prior to Study Entry
2 As indicated per protocol
3 Only for patients who drop out of the Primary Follow-up before Month 60.
4 Patients will be followed for survival until the end of trial, or until they are enrolled in the long-term follow-up.
5 Long term safety follow-up conducted per health authority guidance under a separate protocol

4.1.1 Leukapheresis assessment

Non mobilized leukapheresis products collected from the patient prior to study entry (historical) may be usable for CTL019 manufacturing if collected at an appropriately certified apheresis center and the product is accepted for manufacturing. If a historical leukapheresis product is not available, an apheresis procedure will be scheduled for cell procurement prior to final enrollment. [redacted]

Sample sentinel vials collected from the leukapheresis will be sent to Novartis manufacturing prior or together with the leukapheresis product.

For guidelines on optimal patient timing of apheresis collection, please refer to the Leukapheresis Key Requirements within the [Leukapheresis, Cryopreservation & Scheduling Manual].

[redacted]

Following informed consent, information on the patient's leukapheresis product will be transferred to Novartis manufacturing. Novartis manufacturing will then evaluate the patient's apheresis product for acceptance. Final enrollment is defined as the point at which the patient meets all clinical inclusion/exclusion criteria, and the patient's leukapheresis product is accepted for manufacturing.

Please refer to the Leukapheresis Key Requirements within the [Leukapheresis, Cryopreservation&SchedulingManual] on the recommended procurement, as well as handling and shipment procedures of the apheresis samples to the designated manufacturing facility.

4.2 Definition of end of the study

The end of study is defined as the last patients last visit (LPLV), which is the last patient's Month 60 evaluation, or the time of premature withdrawal. Patients who discontinue the "Treatment and Primary Follow-Up Phase" before month 60 will continue to be followed in the secondary follow-up phase in order to collect health authority requested data (e.g. delayed adverse events) up to 5 years after CTL019 infusion. It is anticipated that patients may leave the primary follow-up and move to secondary follow-up due to reasons including: progression of disease, treatment failure, relapse after remission, pursuing SCT while in remission, or withdrawal from the primary follow-up.

In addition, semiannual and annual evaluations will be performed for up to 15 years from the date of infusion on all patients under a separate long term follow-up (LTFU) protocol as recommended by health authority guidance for patients treated with gene therapies. All patients who either complete or prematurely discontinue from the study will be enrolled in this destination protocol at the time of study completion/discontinuation (a separate informed consent form will be provided for this protocol; Section 7.1.7).

Patients may continue to be followed under the current protocol for survival, pregnancy outcomes and secondary malignancy, which can be conducted via a form or telephone contact until Last Patient Last Visit (LPLV) as defined above or until they choose to enroll into the long term follow-up protocol (CCTL019A2205B), whichever occurs first.

4.3 Early study termination

The study can be terminated at any time for any reason by the sponsor, Novartis, or if any of the stopping criteria described in Section 6.2.4.1.1 are met. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure adequate patient consideration is given to the protection of the patient's interests. For patients who have received CTL019 infusion, a long term post-study follow-up for delayed AEs including monitoring for lentiviral safety will still continue under a separate destination protocol for 15 years post infusion per health authority guidelines. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the early termination of the trial.

[redacted]

5 Population

5.1 Patient population

The study will enroll adult patients ≥ 18 years with relapsed or refractory DLBCL, having failed 2 or more lines of therapy and not eligible for HSCT. A minimum of 25 patients in each of the two most common subtypes of DLBCL: GC and ABC type will be treated in the main study cohort. Patients with T cell rich/histiocyte rich large B cell lymphoma (THRBCL), primary cutaneous DLBCL, primary mediastinal B cell lymphoma (PMBCL), EBV positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma are not allowed.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures
2. Patients must be ≥18 years of age
3. Histologically confirmed DLBCL at last relapse (by central pathology review before enrollment).
   a. Sufficient FFPE tumor samples must be available for histological and molecular subtype testing along with a corresponding pathology report. A recent tumor sample obtained for the purpose of the study must be submitted however if not clinically feasible, an archival tumor biopsy from the most recent relapse may be submitted instead. Excisional biopsies should be submitted wherever possible; in cases where this is not possible, a core needle biopsy is allowable. Fine needle aspiration (FNA) is not allowed.
4. Relapsed or refractory disease after ≥2 lines of chemotherapy, including rituximab and anthracycline, and either having failed autologous HSCT, or being ineligible for or not consenting to autologous HSCT
5. Measurable disease at time of enrollment:
   a. Nodal lesions greater than 20 mm in the long axis, regardless of the length of the short axis
   b. Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) ≥ 10 mm in long AND short axis

   For detailed information please refer to Section 14.1 Guidelines for efficacy evaluation in in diffuse large B cell lymphoma and follicular lymphoma studies [redacted]
6. Life expectancy ≥12 weeks
7. ECOG performance status that is either 0 or 1 at screening

[redacted]

8. Adequate organ function:
   a. Renal function defined as:
      - A serum creatinine of ≤1.5 x ULN OR
      - eGFR ≥ 60 mL/min/1.73 m^2
   b. Liver function defined as:
      - ALT ≤ 5 times the ULN for age
      - Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert–Meulengracht syndrome; patients with Gilbert-Meulengracht syndrome may be included if their total bilirubin is ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN
   c. Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation > 91% on room air
   d. Hemodynamically stable and LVEF ≥ 45% confirmed by echocardiogram or MUGA
   e. Adequate bone marrow reserve without transfusions defined as:
      - Absolute neutrophil count (ANC) > 1.000/mm^3
      - Absolute lymphocyte count (ALC) >300/ mm^3, and absolute number of CD3+ T cells >150/mm^3
      - Platelets ≥ 50.000/mm^3
      - Hemoglobin > 8.0 g/dl
9. Must have an apheresis product of non-mobilized cells accepted for manufacturing.
10. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, and all male participants must use highly effective methods of contraception for at least 12 months following CTL019 infusion and until CAR T cells are no longer present by qPCR on two consecutive tests.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.

BOTH of the following forms of contraception must be utilized:

- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormonal vaginal ring or transdermal hormonal contraception
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Use of intrauterine devices (IUDs) is excluded due to increased risks of infection and bleeding. Placed IUDs may remain in place but additional measures of contraception are mandated.

[redacted]

Additionally, drugs that induce cytochrome P450 (CYP) enzymes can increase the clearance of sex hormones that are eluted by the devices and reduce contraceptive efficacy; given the poly-pharmacy for these patients this presents a real risk of device failure and possible inadvertent resultant conception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

11. Sexually active males must accept to use a condom during intercourse for 12 months after treatment as they should not father a child in this period. A condom is required to be used also by vasectomized men (as well as during intercourse with a male partner or sterile female partner) as WBCs are a normal part of semen and transmission of CTL019 transduced cells may occur.

5.3 Exclusion criteria

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

1. Prior treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
2. Treatment with any prior gene therapy product
3. Active CNS involvement by malignancy
4. Prior allogeneic HSCT
5. Eligible for and consenting to autologous HSCT
6. Chemotherapy other than lymphodepleting chemotherapy within 2 weeks of infusion
7. Investigational medicinal product within the last 30 days prior to screening
   Note: Investigational therapies must not be used at any time while on study until the first progression following CTL019 infusion.
8. The following medications are excluded:
   a. **Steroids:** Therapeutic doses of steroids must be stopped > 72 hours prior to leukapheresis and > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: <12 mg/m^2/day hydrocortisone or equivalent
   b. **Immunosuppression:** Any other immunosuppressive medication must be stopped ≥ 2 weeks prior to leukapheresis and ≥ 2 weeks prior to CTL019 infusion. This could include check point inhibitors (monoclonal antibodies and small molecule modulators).
   c. **Antiproliferative therapies** other than lymphodepleting chemotherapy within 2 weeks of leukapheresis and 2 weeks prior to infusion
      - Short acting drugs used to treat leukemia or lymphoma (e.g. tyrosine kinase inhibitors, and hydroxyurea) must be stopped > 72 hour prior to leukapheresis and > 72 hours prior to CTL019 infusion
      - Other cytotoxic drugs, including low dose daily or weekly maintenance chemotherapy, must not be given within 2 weeks prior to leukapheresis and within 2 weeks prior to CTL019 infusion.

[redacted]

- Fludarabine may be associated with prolonged lymphopenia. This should be taken into consideration when evaluating the optimal timing for leukapheresis collection.

d. **Antibody use** including anti-CD20 therapy within 4 weeks prior to infusion or 5 half-lives of the respective antibody, whichever is longer. Note: Rituximab is excluded within 4 weeks prior to infusion.
e. **CNS disease prophylaxis** must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)

9. Prior radiation therapy within 2 weeks of infusion
10. Active replication of or prior infection with hepatitis B or active hepatitis C (HCV RNA positive)
11. HIV positive patients
12. Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion)
13. Unstable angina and/or myocardial infarction within 6 months prior to screening
14. Previous or concurrent malignancy with the following exceptions:
    a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry)
    b. *In situ* carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study
    c. A primary malignancy which has been completely resected and in complete remission for ≥ 5 years
15. Pregnant or nursing (lactating) women. NOTE: female study participants of reproductive potential must have a negative serum or urine pregnancy test performed within 24 hours before lymphodepletion
16. Intolerance to the excipients of the CTL019 cell product
17. Cardiac arrhythmia not controlled with medical management
18. Removed
19. Prior treatment with any adoptive T cell therapy
20. Patients with T-cell rich/histiocyte rich large B-cell lymphoma (THRBCL), primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), EBV positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma
21. Patients with active neurological auto immune or inflammatory disorders (e.g. Guillain-Barré Syndrome, Amyotrophic Lateral Sclerosis)

6 Treatment

6.1 Study treatment

CTL019 is an autologous cellular immunotherapy product that is comprised of CD3+ T cells that have undergone *ex vivo* T cell activation, gene modification, expansion and formulation in infusible cryomedia. The transgene to be expressed via lentiviral vector transduction is a CAR targeted against the CD19 antigen. The CAR contains a murine scFv that targets CD19 linked

to a transmembrane region derived from the CD8 receptor, which is linked to an intracellular bipartite signaling chain of TCR-ζ (or CD3-ζ) and 4-1BB intracellular signaling domains. The extracellular scFv with specificity for CD19 is derived from a mouse monoclonal antibody. T cells which are enriched from a patient leukapheresis unit are expanded *ex vivo* using commercially available magnetic beads that are coated with anti-CD3 and anti-CD28 monoclonal antibodies. The cells are transduced with the CD19 CAR lentiviral vector which ensures that only peripheral white blood cells enriched for lymphocytes are exposed to the vector. The residual non-integrated vector is washed away during the process. CTL019 cells will be expanded *ex vivo* for up to 10 days. At the end of the culture, the CTL019 cells are depleted of magnetic beads, washed, concentrated, and cryopreserved**.** Results from a release testing procedure are required prior to release of the product for infusion.

6.1.1 Dosing regimen

The target dose of CTL019 transduced cells for adult patients will consist of a single infusion of 5 x 10^8 viable CTL019 transduced cells, which will be administered via intravenous infusion. The acceptable dose range is considered as 1 - 5x10^8 viable CTL019 transduced cells.

6.1.1.1 Lymphodepleting chemotherapy

It is anticipated that many patients will have been receiving chemotherapy for relapsed or resistant disease. Prior to CTL019 cell infusion, an additional lymphodepleting chemotherapy cycle is planned. The use of any additional chemotherapy prior to the recommended lymphodepleting chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden. If patients have a White Blood Cell (WBC) count ≤1,000 cells/μL within one week prior to CTL019 infusion, lymphodepleting chemotherapy is **NOT** required.

When given, lymphodepleting chemotherapy should be started 14 to 5 days before CTL019 infusion (D1) to allow for at least 48 hours from last dose of lymphodepleting chemotherapy to CTL019 infusion. The chemotherapy start date will vary based on the selected chemotherapy. The purpose of this chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CTL019 cells. For lymphodepleting chemotherapy, cyclophosphamide-based regimens are the agents of choice as there is the most experience with the use of these agents in facilitating adoptive immunotherapy. The proposed lymphodepleting regimen is:

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

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

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

Note: Female patients of childbearing potential must have a negative pregnancy test (urine or serum) 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 14 to 5 days before CTL019 infusion (see Table 7-1).

[redacted]

6.1.1.2 CTL019 infusion

The CTL019 cell product will be prepared and released by the manufacturing facility to the study site approximately 4-5 weeks after manufacturing has commenced, provided all required safety and quality release criteria have been met. Upon receipt of the cryopreserved CTL019 cell product, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. The cryopreserved CTL019 cell product should be kept in the vapor phase of liquid nitrogen until CTL019 infusion. For details on the cryopreserved components, and the specific storage and handling requirements of the CTL019 cell product, see the [Investigational Product Handling Manual].

Prior to CTL019 infusion the following criteria must be met:

1. All patients must undergo a rapid influenza diagnostic test within 10 days prior to the planned CTL019 infusion. If the patient is positive for influenza, oseltamivir phosphate or zanamivir should administered for 10 days as preventative treatment (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their 10 day preventative treatment course **prior** to receiving CTL019. The test does not need to be repeated prior to CTL019 infusion however, if flu-like or respiratory signs and symptoms are present, CTL019 infusion should be delayed until the patient is asymptomatic.
   For patients residing in the United States, Canada, Europe and Japan, influenza testing is required during the months of October through May (inclusive). For patients residing in the southern hemisphere such as Australia, influenza testing is required during the months of April through November (inclusive). For patients with significant international travel, both calendar intervals above may need to be considered.
2. Patient should not experience a significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with experimental cell infusion. CTL019 infusion should be delayed in such cases.
3. Rapidly progressing patients, or patients experiencing laboratory abnormalities after enrollment, that in the opinion of the treating investigator or PI may impact patient safety or the patients' ability to receive the CTL019 infusion, may have their infusion delayed until both the treating investigator and PI determine it is clinically appropriate to proceed with the CTL019 infusion.
4. Patients experiencing toxicities from their preceding lymphodepleting chemotherapy will have their infusion schedule delayed until these toxicities have resolved. The specific toxicities warranting delay of CTL019 cell infusion include:
   a. Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 91% or presence of progressive radiographic abnormalities on chest x-ray
   b. Cardiac: Cardiac arrhythmia not controlled with medical management
   c. Hypotension requiring vasopressor support
   d. Uncontrolled active infection, as evidenced by positive blood cultures for bacteria, fungus, or PCR positivity for viral DNA in blood within 72 hours of CTL019 cell infusion, or clinical or radiographic evidence

[redacted]

5. Following lymphodepleting chemotherapy patients must not have progressive disease in order to receive CTL019 infusion, as this will potentially put them at an unacceptable risk for severe CRS. Patients should not receive CTL019 infusion if they exhibit significant progression of disease following lymphodepleting chemotherapy as evidenced by:
   a. Significant increase in nodal disease
   b. Significant increases in extranodal areas
   c. Occurrence of new lymphoma manifestations
   d. Clinical evidence of CNS disease
6. If patients are taking any of the following medications, their infusion must be delayed until the medications have been stopped according to the below:
   a. Steroids: Therapeutic doses of steroids must be stopped >72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: < 12 mg/m^2/day hydrocortisone or equivalent
   b. Antiproliferative therapies other than the protocol specified lymphodepleting therapy must have been stopped ≥ 2 weeks prior to CTL019 infusion
   c. Short acting drugs used to treat leukemia or lymphoma (e.g. tyrosine kinase inhibitors, and hydroxyurea) must be stopped > 72 hour prior to leukapheresis and > 72 hours prior to CTL019 infusion. Other cytotoxic drugs, including low dose daily or weekly maintenance chemotherapy, must not be given within 2 weeks prior to leukapheresis and within 2 weeks prior to CTL019 infusion.
   d. Immunomodulatory drugs must be stopped ≥ 2 weeks prior to infusion. This could include check point inhibitors (monoclonal antibodies and small molecule modulators).
   e. Antibodies including anti-CD20 therapy must be stopped ≥ 4 weeks prior to infusion or 5 half-lives of the respective antibody prior to infusion, whichever is longer. Note: Rituximab is excluded within 4 weeks prior to infusion.
   f. CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate).

Patients experiencing toxicities from their preceding chemotherapy will have their CTL019 infusion delayed until the above toxicities have been resolved. If any of the above criteria are not met and a period of delay is 4 or more weeks from completing lymphodepleting chemotherapy and the WBC>1000/μL, the patient will need to be re-treated with lymphodepleting chemotherapy, and these criteria will need to be re-established prior to CTL019 infusion.

Additional safety procedures prior to administration:

The risk of tumor lysis syndrome (TLS) is dependent on disease burden. Patients will be closely monitored both before and after lymphodepleting chemotherapy and CTL019 infusions including blood tests for potassium and uric acid. Patients with elevated uric acid or high tumor burden will receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat). Infection prophylaxis should follow local guidelines dictated only by the preceding lymphodepleting chemotherapy. Infection prophylaxis *per se* for CTL019 is not recommended.

[redacted]

The site must confirm that two doses of tocilizumab are on site prior to CTL019 infusion and one dose of siltuximab (if available in country) must be accessible within 24 hours of infusion for administration in order to manage suspected toxicities. (see Section 6.2.4.2.1 for details).

Premedication:

Side effects from T cell infusions can include fever, chills and/or nausea. All patients should be pre-medicated with acetaminophen or paracetamol and diphenhydramine or another H1 antihistamine. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved with acetaminophen or paracetamol. Steroids should NOT be used for premedication. It is recommended that patients NOT receive systemic corticosteroids other than physiologic replacement of hydrocortisone at any time, except in the case of life threatening emergency, since this may have an adverse effect on CTL019 cell expansion and function.

[redacted]

Following CTL019 infusion: Should emergency treatment be required in the event of life-threatening hypersensitivity or other acute infusion-related reaction, supportive therapy such as oxygen, bronchodilators, epinephrine, antihistamines, and corticosteroids should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Supportive care: Local guidelines will be followed for the supportive care of immunosuppressed and chemotherapy treated patients including infection management. All blood products administered should be irradiated. Immunosuppressive medications, including steroids, should not be administered unless life threatening circumstances arise.

6.1.2 Ancillary treatments

As side effects from T cell infusions can include fever, chills and/or nausea, all patients should be pre-medicated with acetaminophen or paracetamol and diphenhydramine or an H1 antihistamine, as described above in Section 6.1.1.2. If fever develops please follow your institutional guidelines for patients with fever/neutropenia and strongly consider admission for close observation.

6.1.3 Rescue medication

Rescue medications are medications given for severe CRS due to CTL019 therapy (Figure 6-1). CTL019 administration may require tocilizumab (recommended dose 8 mg/kg i.v.), steroids, and siltuximab (11 mg/kg IV over 1 hour) for the treatment of suspected CRS toxicities as described below in Section 6.2.4.2.1.

The site must confirm that two doses of tocilizumab are on site and available for administration prior to CTL019 infusion and one dose of siltuximab (if available in country) must be accessible within 24 hours of infusion. (see Section 6.2.4.2.1 for details). All rescue medications (except for tocilizumab or siltuximab), including steroids given to treat CRS, must be listed on the concomitant medication CRF. Tocilizumab or siltuximab therapy administration should be reported on the "Dose Administration Record - Tocilizumab" or "Dose Administration record - Siltuximab" eCRF, respectively. Steroids given to treat CRS must be listed on the concomitant medication CRF.

6.1.4 Guidelines for continuation of treatment

Not applicable

6.1.5 Treatment duration

A single dose of CTL019 transduced cells will be given.

6.2 Dose escalation guidelines

Not applicable

6.2.1 Starting dose rationale

Not applicable

[redacted]

6.2.2 Provisional dose levels

Not applicable

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

Not applicable

6.2.3.1 Implementation of Dose Escalation Decisions

Not applicable

6.2.3.2 Intra-Patient dose escalation

Not applicable

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

6.2.4.1 Toxicity management, stopping rules and study termination

It is expected that AEs will occur frequently in this population based on the underlying advanced malignancy and that these can be SAEs. Therefore, there is no specific occurrence of SAEs that define a stopping rule, but the review of SAEs will form the basis for potential early stopping of the study. Only unexpected SAEs that are related to the CTL019 transduced cells would define a stopping rule. The review of these adverse events, and any decision to prematurely stop patient enrollment, will be determined by the Data Monitoring Committee (DMC) and reviewed by the IRB.

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

6.2.4.1.1 Criteria for stopping or pausing the study

During the **safety run-in stage** the study will be paused, and health authorities notified, if at least one of the following events occur:

- Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to CTL019 therapy. High fevers, hypotension, hypoxia, disseminated intravascular coagulation, encephalopathy (e.g. lethargy, confusion, aphasia, seizures), intensive care unit (ICU) admission, dialysis and mechanical ventilation are expected. The expected side effects can also result in grade 4 liver toxicity, nephrotoxicity and other organ involvement
- Death suspected to be related to CTL019 therapy

After the safety run-in stage the study may be paused pending notification of the health authorities and the DMC for investigation and possible protocol amendment if any patient experiences any of the following events within three weeks of the CTL019 cell infusion:

[redacted]

- Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to CTL019 therapy.
    - High fevers, hypotension, hypoxia, disseminated intravascular coagulation, encephalopathy (e.g. lethargy, confusion, aphasia, seizures), intensive care unit (ICU) admission, dialysis and mechanical ventilation are expected. The expected adverse effects can also result in grade 4 liver toxicity, nephrotoxicity and other organ involvement.
- Death suspected to be related to CTL019 therapy
- Any patient develops uncontrolled T cell proliferation beyond 8 weeks from CTL019 cell product infusion that does not respond to management
- Any patient develops detectable replication competent lentivirus (RCL) during the study
- The Investigator, Sponsor, DMC, or any independent review board or regulatory body decides for any reason that patient safety may be compromised by continuing the study
- The Sponsor decides to discontinue the development of the intervention to be used in this study

6.2.4.2 General toxicity management considerations

Patients treated with CTL019 should not donate blood, organs, tissues, sperm, oocytes and cells.

6.2.4.2.1 Expected toxicities

Acute Infusion reaction

Acetaminophen/paracetamol and diphenhydramine/H1 antihistamine may be repeated every 6 hours as needed. A course of non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved by acetaminophen/paracetamol. It is recommended that patients not receive corticosteroids at any time, except those already on physiologic replacement therapy, or in the case of a life threatening emergency, since this may have an adverse effect on CTL019 cells.

Cytokine Release Syndrome (CRS) / Macrophage Activation Syndrome (MAS)

Data from CTL019 treated patients experiencing CRS show marked elevations in IL-6 and IFN-g. The symptoms generally occur 1-14 days after cell infusion and may include high fevers, rigors, myalgia/arthralgias, nausea/vomiting/anorexia, fatigue, headache, encephalopathy, hypotension, dyspnea, tachypnea and hypoxia. Renal failure/renal injury, hyperbilirubinemia and increased ALT or AST can also occur. Supportive care and anti-cytokine therapy have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most patients; Several patients with a suboptimal response to the first dose of tocilizumab have received a second or third dose of tocilizumab with CRS resolution. In patients with incomplete resolution of CRS after several doses of tocilizumab, CRS resolution has been observed following siltuximab administration. [redacted] Fatal outcomes

[redacted]

associated with CRS have been observed in adult ALL patients in the context of current significant clinical infections. Findings from study UP13413 could imply a higher risk to develop CRS in patients with bone marrow involvement (Schuster, unpublished data). Accordingly, patients with lymphoma involving the bone marrow should be monitored even more closely for signs of CRS.

A detailed treatment algorithm has been established with clear criteria for CRS management and guidance on when to administer tocilizumab and siltuximab as presented below in Figure 6-1 and must be followed by investigators. Tumor necrosis factor (TNF alpha) antagonists have been used with CTL019 associated CRS with little evidence for efficacy. Given the apparent lack of activity combined with their immunosuppressive effects, TNF antagonists are not recommended. This approach was designed to avoid life-threatening toxicities, while attempting to allow the CTL019 transduced cells to establish a proliferative phase which appears to correlate with tumor response. Patients will be required to remain proximal to the treating site for the first 21 days.

The management of CRS is based solely upon clinical parameters as described in Figure 6-1 below. [redacted] Cases of transient left ventricular dysfunction, as assessed by echocardiogram (ECHO), have been reported in some patients with severe (Grade 4) CRS. Therefore consideration should be given to monitoring cardiac function, by ECHO, during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

Clinically significant coagulopathy is often seen with moderate to severe CRS (Grade 3 and 4) and may continue as CRS is beginning to clinically resolve. Coagulation parameters (PT, aPTT, and fibrinogen) should be more frequently monitored in this setting. CTL019 associated coagulopathy with or without clinical bleeding and hypofibrinogenemia is strongly recommended to be managed with cryoprecipitate of fibrinogen concentrate in addition to routine blood product support.CTL019 related CRS can be associated with neurologic events. Two types of neurologic events with respect to timing of onset have been observed. Onset of neurologic events can be concurrent with high fevers during the development and maximal grade of CRS. Delayed onset of neurologic events can also occur as CRS is resolving or after CRS has completely resolved. Consideration should be given to monitoring for neurologic events during and after resolution of CRS.

A modification of the Common Terminology Criteria for Adverse Events (CTCAE) CRS grading scale has also been established to better reflect CTL019-therapy-associated CRS as presented in Table 6-1.

Specific CRFs have been developed for the capture of CRS elements, severity, management and response to intervention.

[redacted]

Figure 6-1 CRS Management Algorithm

Pretreatment

Acetaminophen/paracetamol and diphenhydramine /H1 anti-histamine

Prophylaxis for complications of TLS as appropriate

CTL019 infusion

Prodromal syndrome: low grade fevers, fatigue, anorexia (hours to days)

Observation, rule out infection (surveillance cultures)

Antibiotics per local guidelines (febrile neutropenia)

Symptomatic support

Symptom progression: High fevers, hypoxia, mild hypotension

1st Line Management:

Oxygen, fluids, low dose vasopressor support, antipyretics

Monitor/manage complications of TLS

Further symptom progression:

- Hemodynamic instability despite intravenous fluids and moderate to "high dose" vasopressor[1] support

OR

- Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow Oxygen (O2) and/or need for mechanical ventilation OR
- Rapid clinical deterioration

2nd Line Management:

Tocilizumab: IV infusion over 1 hour

- Patient weight < 30 kg: 12 mg/kg i.v.
- Patient weight ≥ 30 kg: 8 mg/kg i.v. (max dose 800 mg)

Hemodynamic and respiratory support

Lack of clinical improvement while awaiting tocilizumab response

3rd Line Management:

Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)

If no improvement within 1st dose of tocilizumab within 12 to 18 hours, consider steroids (plan rapid taper after hemodynamic normalization):

2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day. As steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement

If no response to steroids within 24 hours, consider 2nd dose of Tocilizumab (dosed as above)

Hemodynamic and respiratory support

Lack of clinical improvement while awaiting response to 3rd line management

4th Line Management:

Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)

If no response to steroids and 2nd dose of tocilizumab within 24 hours or further clinical deterioration, consider siltuximab 11 mg/kg IV over 1 hour (if available in country).

Hemodynamic and respiratory support

Lack of clinical improvement while awaiting response to 4th line management

5th Line Management:

Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)

In ongoing CRS despite prior therapy, consider anti-T cell therapies such as cyclophosphamide, anti-thymocyte globulin, or alemtuzumab

Hemodynamic and respiratory support

[1] See specific definition of "high dose" vasopressors in Table 6-2 below

[redacted]

Table 6-1 CTL019 therapy associated grading for cytokine release syndrome: The Penn Grading Scale for Cytokine Release Syndrome (PGS-CRS)

● Marked elevations in IL-6, interferon gamma and less intensely TNF ● Symptoms occur 1 to 14 days after cell infusion ● Symptoms may include: high fever, rigors, myalgia, arthralgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea and hypoxia			
1	**2**	**3**	**4**
Mild reaction: Treated with supportive care such as antipyretics and antiemetics.	Moderate reaction: Requiring intravenous therapies or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests [LFTs]) related to CRS and not attributable to any other condition. Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids or low dose vasopressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.	Life-threatening complications such as hypotension requiring high dose vasopressors (see Table 6-2) or hypoxia requiring mechanical ventilation.

[redacted]

Table 6-2 High dose vasopressor use

Definition of "High-Dose" Vasopressors	
Vasopressor	Dose for ≥ 3 hours
Norepinephrine monotherapy	≥ 0.2 mcg/kg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200mcg/min
Epinephrine monotherapy	≥ 0.1 mcg/kg/min
If on vasopressin	High-dose if vaso + Norepinephrine Equivalent (NE) of ≥0.1 mcg/kg/min (using Vasopressin and Septic Shock Trial (VASST) formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 mcg/min (using VASST formula)
Vasopressin and Septic Shock Trial (VASST) Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10] Criteria from Russell et al (2008)	

Tumor lysis syndrome

Close monitoring for TLS before and after chemotherapy and CTL019 infusions, including blood tests (potassium, uric acid, etc.) will be done as follows:

- **Screening phase**:
  - Prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat), and increased oral/ IV hydration prior to lymphodepleting chemotherapy and CTL019 infusion should be given in patients with elevated uric acid or high tumor burden
  - Early and prompt implementation of supportive care in case of symptoms of acute TLS (i.v. hydration and rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)
- **Post-infusion monitoring phase**:
  - Frequent monitoring of the following laboratory tests (2 to 3 times/week for 3 weeks from start of lymphodepleting chemotherapy, then weekly): potassium, phosphorus, calcium, creatinine, and uric acid
  - Encourage oral hydration
  - Laboratory and clinical TLS is defined as follows:

Laboratory TLS is defined as two or more of the following values within three days before or in the days following CTL019 infusion.

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

If zero or one of the laboratory values above are abnormal, continue to manage with allopurinol or a non-allopurinol alternative (e.g. febuxostat) and oral hydration. Consider IV fluids and rasburicase if uric acid levels remain elevated, and consider in hospital monitoring.

[redacted]

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

Clinical TLS is defined as the presence of laboratory TLS plus ≥ 1 of these criteria in the absence of other causes.

- Serum creatinine ≥ 1.5 times the upper limit of normal range
- Symptomatic hypocalcemia
- Cardiac arrhythmia

If Clinical TLS exists, manage with IV fluids, laboratory blood tests every 6 to 8 hours, cardiac monitoring, rasburicase/allopurinol/febuxostat and inpatient care (consider ICU)

Criteria modified from Cairo and Bishop (2004).

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 therapy including CTL019 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.

In clinical trials, the majority of neurological events following CTL019 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.

[redacted]

Notably, the onset of neurological events after CTL019 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.

The causality assessment of neurological events in patients treated with CTL019 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.

Prolonged depletion of normal B cells and hypogammaglobulinemia

Based on previous clinical experience, it is likely that CTL019 therapy will result in B cell depletion and hypogammaglobulinemia. Experience with CTL019 therapy shows that patients with persistent B cell aplasia demonstrate hypogammaglobulinemia which has been managed with immunoglobulin therapy. In the event of hypogammaglobulinemia, patients should be considered for immunoglobulin therapy per local clinical practice guidelines.

Infections and infectious complications

Depletion of B cells with resulting hypogammaglobulinemia is expected as a result of CTL019 on target effects. CTL019 related hypogammaglobulinemia is typically managed with immunoglobulin replacement therapy dependent upon age specific, disease specific and local institutional guidelines. Immunoglobulin replacement during the study period will be recorded. In general B cell aplasia and hypogammaglobulinemia, of various causes, can be associated with increased rates of infection. Such infections are typically sinopulmonary but other sites and types of infections have also been reported.

Institutional guidelines for vaccination (e.g. pneumococcus) should be followed before starting CTL019 therapy. No live vaccines should be used in CTL019 recipients or prospective recipients as the lack of effective B cells after infusion makes the likelihood of a systemic infection considerable and the value negligible.

Other potential complications of B cell aplasia include progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B virus.

For the first 12 months of the study, all data on infections will be collected for patients in the primary follow-up. After 12 months for CTL019 treated patients or if patients move to the secondary follow-up, data on infections will only be collected when they are opportunistic or serious and requiring intervention as defined:

1. Requires anti-infective treatment
2. Leads to significant disability or hospitalization
3. Needs surgical or other intervention

Viral Reactivation

Patients with active hepatitis B or active hepatitis C have been excluded from clinical studies with CTL019, because of the potential risk of viral reactivation and the risk of fulminant hepatitis, hepatic failure and fatal outcome. HIV positive patients have been also excluded, because of the possible effect on HIV viral suppression.

[redacted]

In addition, there is currently no experience with manufacturing CTL019 for patients testing positive for HBV, HCV and HIV. Patients are to be screened for any active HBV, HCV or HIV infection prior to leukapheresis.

Subjects with active hepatitis B or hepatitis C or subjects with HIV confirmed by serology will not be enrolled in the study.

Hematological disorders including cytopenias

The etiology of cytopenias is multifactorial, likely reflecting a combination of effects from the underlying disease, cytotoxicity from prior anticancer treatment, bridging chemotherapy during the CTL019 manufacture waiting time and conditioning lymphodepleting chemotherapy just prior to CTL019 infusion in addition to the CAR-T cell therapy per se, which is frequently associated with B-cell aplasia as on-target effect. Prolonged hematological cytopenias and hematological disorders are considered a sequelae.

6.2.4.2.2 Potential toxicities

Cerebral Edema

Five fatal cases of cerebral edema occurred in the ROCKET study in adult ALL treated with JCAR015 and were characterized by a rapid evolution soon after JCAR15 infusion appeared to be resistant to anti-cytokine treatment, and ensued brain death within 1-2 days after diagnosis.

[redacted]

No fatal cerebral edemas have been reported following CTL019 infusion in the clinical development program or the post-marketing setting to date that would resemble the clinical course reported for JCAR015. JCAR015 presents a different construct of an anti-CD19 CAR-T-cell product compared to CTL019.

Replication-competent lentivirus (RCL) testing

Replication-competent lentivirus (RCL) may be generated during CTL019 manufacturing using a lentiviral vector to encode anti-CD19 CAR or subsequently after introduction of vector transduced viable T cells into the patient. However, 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 CTL019 and the negligible probability of de novo generation of any RCL. None of the subjects tested in the development program showed evidence of RCL. However, generation of an RCL following CTL019 infusion remains a theoretical possibility. The development of RCL could pose a risk to patients and therefore, monitoring for RCL will be conducted during the course of the trial (see Product Handling Manual for a description of the assays). Blood samples for RCL testing will be collected as per Table 7-1. If blood samples test are negative through Month 12, all samples taken after Month 12 will be stored for potential future testing. Additional, unscheduled samples for RCL testing, for persistence testing of CAR transgene sequences, and/or for B and T-cell enumeration can be collected anytime on a case-by-case basis. If a positive RCL assay

[redacted]

result is obtained from a patient blood specimen, (as detected by Vesicular Stomatitis Virus/Glycoprotein (VSV-G) qPCR, for example) the Investigator will be informed and the patient rescheduled for a retest of the DNA test. ,

As per guidance for gene therapy medicinal products, patients exposed to CTL019 will be monitored for 15 years following last treatment for vectors persistence and RCL within the long-term follow-up study. In case of suspected secondary malignancies, as per the guidance "Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up" (FDA 2020), biopsy sample of neoplastic tissues or relevant autopsy tissues will be collected for RCL testing.

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 detection following CTL019 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.

[redacted]

CTL019 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.

CTL019 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

[redacted]

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 CTL019.

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 CTL019 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).

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

For the follow-up of secondary malignancy, please refer to Section 8.10.

CTL019

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

If a patient develops a condition that precludes CTL019 infusion after enrollment but before infusion, the patient will be prematurely discontinued. This will be done at the judgment of the PI, and could include for example, the occurrence of an intercurrent illness requiring the institution of systemic immunosuppression.

6.2.6 Concomitant Therapy

Clinically significant prescription and nonprescription medication, excluding vitamins, and herbal and nutritional supplements, and procedure-related (inpatient or outpatient) medications taken by the patient during the 30 days prior to screening will be recorded. At every visit following the screening visit up to the month 60 visit, concomitant medications will be recorded in the medical record and on the appropriate CRF.

During selected trial phases concomitant medication collection will be modified as outlined in Appendix 3: CTL019 Modified Data Reporting- Treatment and Primary Follow Up Phase, Appendix 4: CTL019 modified data reporting – Secondary Follow Up Phase, CRF Completion Guidelines (CCGs), and Table 6-3 below. Modified collection of concomitant medications during these periods are designed to capture CTL019-related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented.

[redacted]

Table 6-3 Concomitant medication reporting by study period

Study period	Inpatient/ICU	Outpatient
Pre-treatment period (ICF to LD chemo/pre-infusion)	Modified	Modified
Treatment period (LD chemo/pre-infusion through M12)	Modified	All concomitant medications
Post-treatment period (after M12 through M60)	Modified	Modified

The following guidelines must be adhered to during the study:

- Granulocyte macrophage-colony stimulating factor (GM-CSF) should be avoided due to the potential to worsen CRS symptoms. Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of CTL019 infusion and long acting G-CSF should not be given within 10 days of CTL019 infusion. The effects of granulocyte colony stimulating factor (G-CSF) on the other hand, are unknown.
- Steroids or other immunosuppressant drugs should NOT be used as pre-medication for CTL019 therapy (refer to Section 6.1.1.2) or following CTL019 infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances. Use of steroids with blood product administration should be eliminated just prior to and following CTL019 if possible or at least minimized.
- Patients with moderate to severe signs and symptoms attributable to CRS should be managed with supportive care and administration of tocilizumab as defined in Figure 6-1 and Section 6.2.4.2.

6.2.7 Prohibited concomitant therapy

The following medications are excluded:

a. **Steroids:** Therapeutic doses of steroids must be stopped > 72 hours prior to leukapheresis and > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: <12 mg/m^2/day hydrocortisone or equivalent

b. **Immunosuppressive therapies:** Any drug used for immunosuppression must be stopped ≥ 2 weeks prior to leukapheresis and ≥ 2 weeks prior to CTL019 infusion. This could include check point inhibitors (monoclonal antibodies and small molecule modulators).

c. **Antiproliferative therapies** other than lymphodepleting chemotherapy within 2 weeks of leukapheresis and 2 weeks prior to infusion.
   - Short acting drugs used to treat leukemia or lymphoma (e.g. tyrosine kinase inhibitors, and hydroxyurea) must be stopped > 72 hour prior to leukapheresis and > 72 hours prior to CTL019 infusion
   - Other cytotoxic drugs, including low dose daily or weekly maintenance chemotherapy, must not be given within 2 weeks prior to leukapheresis and within 2 weeks prior to CTL019 infusion.
   - Fludarabine may be associated with prolonged lymphopenia. This should be taken into consideration when evaluating the optimal timing for apheresis collection.

Antibody use including anti-CD20 therapy within 4 weeks prior to infusion or 5 half-lives of the respective antibody, whichever is longer. Note: Rituximab is excluded within 4 weeks prior to infusion.

[redacted]

d. **CNS disease prophylaxis** must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)
e. **Investigational therapies** must not be used at any time while on study until the first progression following CTL019 infusion**.**

6.3 Dose modifications

6.3.1 Dose modification and dose delay

Not applicable

6.3.2 Follow-up for toxicities

6.3.2.1 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational treatment, a standardized process for identification, monitoring and evaluation of liver events has to be followed.Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of elevated transaminases and/or bilirubin (elevated liver function tests (LFTs))
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and / or pre-specified adverse events.

Please refer to Appendix 5 Section 14.5.1 for complete definitions of liver events.

Any liver event which meets the criteria for "**medically significant**" event as outlined in Appendix 5 Section 14.5.1 should follow the **standard procedures for SAE reporting** as described in Section 8.2.

Every liver event as defined in Appendix 5 Section 14.5.1 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Appendix 5 Section 14.5.2. .

- Repeating the LFT to confirm elevation as appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages.

For additional details please refer to Section 6.2.4

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

Subjects with transaminase increase combined with total bilirubin increase may be indicative of potential DILI and should be considered as clinically important events.

[redacted]

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

- For subjects with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For subjects with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever occurs first, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any preexisting liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-4 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

[redacted]

Table 6-4

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1 antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of a serious adverse event (SAE) and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.3.2.3 Renal safety monitoring

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

1. Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
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 (*select as applicable:* for Phase 2 and Phase 3).

Every renal laboratory trigger or renal event should be followed up by the investigator or designated personnel at the trial site as summarized in Section 14.6.1 (Specific Renal Alert Criteria and Actions) in Appendix 6.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Upon informed consent completion, the patient will initiate screening. Each patient is identified in the study database by a Subject Number (Subject No.), that is assigned sequentially at each site by IRT when the patient is first enrolled for screening and is retained as the primary

[redacted]

identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the four digit Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential three digit patient number suffixed to it, so that each subject is numbered uniquely across the entire database.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. 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 patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the appropriate CRF page.

IRT must be notified within 2 days that the patient was not treated.

6.4.2 Treatment assignment

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

6.4.3 Treatment blinding

This is an open-label study.

[redacted]

[redacted]

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments through the end of the Treatment and Primary Follow-up phase (Section 7.1.1, Section 7.1.2 and Section 7.1.3). For patients who discontinue early from the Treatment and Primary Follow-Up Phase prior to Month 60, the patient will enter an observational Secondary Follow-Up Phase to collect health authority requested data (e.g. delayed adverse events, etc.). The first visit in the Secondary Follow-Up Phase is determined according to the time when the patient discontinued from the Treatment and Primary Follow-Up Phase since CTL019 infusion. For example, if the patient discontinued from the Treatment and Primary Follow-Up phase at Month 10, the first visit in the Secondary Follow-Up Phase will be Month 12. Table 7-2 lists all of the assessments through the end of the Secondary Follow-up phase (Section 7.1.4).

In each table, required assessments are indicated with an "X" at the visits when they are performed. The letter (D) in Table 7-1 and Table 7-2 under the category column indicates the assessments that will have data entered into the clinical database and (S) is for assessments that will have data remain as source documentation. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used in the patient's source documentation.

Table 7-1 Primary visit evaluation schedule

Phase				Pre-Treatment			Treatment and Primary Follow-up															Survival Follow-up after study completion
Visit Name	Category	Protocol Section	Screening	Enrollment/Pre-	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post-infusion													End of Treatment and Primary Follow-up	
Study day			W-8 to W-4	W-3 to D-8	W-2 to D-5	D -1	D1	D2	D4 ±1d	D 7 ±1d	D 11 ±1d	D 14 ±1d	D 17 ±1d	D 21 ±3d	D 28 ±7d	M2 M3 M4 M5 M6 ±14d	M9 M12 ±14d	M18 M24 ±14d	M30 M42 M54 ±14d	M36 M48 ±14d	M60 ±14d	q 3m
Obtain Informed Consent	D	7.1.1	X																			
IWRS/IRT Registration	S		X	X			X														X	
Patient history																						
Demography	D	7.1.1	X																			
Inclusion/exclusion criteria	D	5.2 5.3	X																			
Medical history	D	7.1.1	X																			
Prior antineoplastic therapy	D	7.1.1	X																			
Prior/concomitant medications	D	6.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Concomitant medications (selected)	D	6.2.6																X	X	X	X	

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up															
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**												**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
Antineoplastic therapies after CTL019 infusion	D	7.1.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Central confirmation of diagnosis and subtype determination (FFPE tumor biopsy)	D	7.2.1	X																			
[redacted]																						
Physical assessments																						
Physical examination	S	7.2.2.1	X			X	X	X		X		X		X	X	X	X	X	X	X	X	
Performance status	D	7.2.2.4	X			X	X	X		X		X		X	X	X	X	X	X	X	X	
Height	D	7.2.2.3	X																			
Weight	D	7.2.2.3	X		X		X								X	X	X	X	X	X	X	
Vital signs	D	7.2.2.2	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up															
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**													**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
Pulse oximetry	D	7.2.2.2	X				X	X	X	X	X	X										
MUGA/ECHO	D	7.2.2.6	X																			
Electrocardiogram (ECG)	D	7.2.2.6	X				X															
Intervention																						
Leukapheresis	D	4.1.1	X																			
Leukapheresis pre-evaluation and acceptance	S	4.1.1	X																			
Lymphodepleting chemotherapy	D	6.1.1.1			X																	
CTL019 infusion prerequisite assessment	S	6.1.1.2					X															
CTL019 transduced cell infusion	D	6.1.1.2					X															

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up														
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**												**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
Efficacy assessments																					
B-symptoms	D	7.2.1	X		X										X	X M3 &M6 only	X	X	X	X	X	
Imaging (CT/MRI)	D	7.2.1	X		X (if no PET-CT)										X	X M3 (if no PET CT) & M6 only	X	X		X	X	
Imaging (PET-CT)	D	7.2.1			X (within 4 weeks prior to infusion)											X M3 only						

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up														
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**												**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
Local response assessment	D	7.2.1			X										X	X M3 & M6 only	X	X		X	X	
Bone marrow biopsy and/or aspirate	D	7.2.1	X												X only if CR and if prior BM involvement	X M3 only	At time of radiological CR					
CSF cytology	D	7.2.1	X		As clinically indicated																	
CNS Imaging (CT/MRI)	S	7.2.1	As clinically indicated																			

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up															
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**													**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
Safety assessments																						
Adverse events	D	8.1 8.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Protocol defined Adverse events and AEs of special interest, including new malignancies	D	8.1 8.2																X	X	X	X	
Pregnancies	D	7.2.2														X	X	X	X	X	X	
Laboratory assessments																						
Hematology	D	7.2.2.5	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	D	7.2.2.5	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Central flow cytometry before leukapheresis (peripheral blood)	D	7.1.1	X																			

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up															
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**													**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
Central flow cytometry (fresh leukapheresis product)	D	7.1.1	X																			
Pregnancies	D	7.2.2.5	X		X														X	X	X	
Serum or Urine pregnancy test	S	7.2.2.5																	X	X	X (Serum)	
Viral serology (CMV, EBV, HIV, HbsAg, HBsAb, HBcAb, HCV RNA)	D	7.2.2.5	X																			
Coagulation (PT, aPTT, INR, fibrinogen, D-dimer)	D	7.2.2.5	X				X			X		X			X							
Serum immunoglobulin levels (IgG, IgA, IgM)	D	7.2.2.5	X			X						X			X	X M3 &M6 only	X				X	

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up														
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**												**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
Urinalysis	D	7.2.2.5	X																		
Rapid Influenza (A and B) Testing	D	6.1.1.2 7.1.2 7.2.2.5		Within 10 days of infusion																	

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up														
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**												**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
CTL019 PK, [redacted] and safety assessments																					
Serum (immunogenicity, cytokines, etc.)	D	7.2.3 7.2.4		X		X		X	X	X	X	X	X	X	X	X M3 &M6 only	X M12 only	X M24 only		X M36 only	X
[redacted]																					

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up															
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**													**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
CTL019 [redacted]	D	7.2.3						see (Table 7-14, Table 7-15)														
CTL019 pharmacokinetics by qPCR (peripheral blood)	D	7.2.3		X			X	X	X	X	X	X	X	X	X	X M2 M3 M6 only	X	X	X	X	X	
CTL019 pharmacokinetics by flow cytometry (peripheral blood)	D			X			X		X	X	X	X	X	X	X	X M2 M3 M6 Only	X	X M18 only			X	

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up														
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**												**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
Tumor biopsy	D	7.2.3 7.2.4	X													X M3 only	As clinically indicated					
CTL019 pharmacokinetics - CSF (CTL019 PK, [redacted])	D	7.2.3	X												As clinically indicated							
CTL019 pharmacokinetics - Bone marrow (CTL019 PK by qPCR)	D	7.2.3	X												X only if CR	X M3 only	As clinically indicated					
CTL019 pharmacokinetics - Bone marrow (flow cytometry)	D	7.2.3	X												X only if CR	X M3 only	As clinically indicated					
[redacted]																						

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up														
Visit Name	Category	Protocol Section	Screening	Enrollment/Pre-	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post-infusion												End of Treatment and Primary Follow-up	Survival Follow-up after study completion
Study day			W-8 to W-4	W-3 to D-8	W-2 to D-5	D -1	D1	D2	D4 ±1d	D 7 ±1d	D 11 ±1d	D 14 ±1d	D 17 ±1d	D 21 ±3d	D 28 ±7d	M2 M3 M4 M5 M6 ±14d	M9 M12 ±14d	M18 M24 ±14d	M30 M42 M54 ±14d	M36 M48 ±14d	M60 ±14d	q 3m
[redacted]																					
RCL by VSV-g q-PCR	D	7.2.2.5		X												X M3 &M6 only	X M12 only	X M24 only		X	X	
Leukapheresis sample for correlative studies	D	7.1.2		X																		
CTL019 cell product sample for correlative studies	D	7.1.2		X																		

[redacted]

Phase				Pre-Treatment			Treatment and Primary Follow-up														
Visit Name	Category	Protocol Section	Screening	Enrollment/Pre-	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post-infusion												End of Treatment and Primary Follow-up	Survival Follow-up after study completion
Study day			W-8 to W-4	W-3 to D-8	W-2 to D-5	D -1	D1	D2	D4 ±1d	D 7 ±1d	D 11 ±1d	D 14 ±1d	D 17 ±1d	D 21 ±3d	D 28 ±7d	M2 M3 M4 M5 M6 ±14d	M9 M12 ±14d	M18 M24 ±14d	M30 M42 M54 ±14d	M36 M48 ±14d	M60 ±14d	q 3m
[redacted]																					

Phase				Pre-Treatment			Treatment and Primary Follow-up														
Visit Name	**Category**	**Protocol Section**	**Screening**	**Enrollment/Pre-**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post-infusion**												**End of Treatment and Primary Follow-up**	**Survival Follow-up after study completion**
Study day			**W-8 to W-4**	**W-3 to D-8**	**W-2 to D-5**	**D -1**	**D1**	**D2**	**D4 ±1d**	**D 7 ±1d**	**D 11 ±1d**	**D 14 ±1d**	**D 17 ±1d**	**D 21 ±3d**	**D 28 ±7d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M18 M24 ±14d**	**M30 M42 M54 ±14d**	**M36 M48 ±14d**	**M60 ±14d**	**q 3m**
[redacted]																					
Survival follow-up	D	7.1.5					For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, whichever comes first. If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact														X
End of phase disposition	D	n/a	X			X														X	

[redacted]

Table 7-2 Secondary follow-up visit evaluation schedule (for patients who end their primary follow up before M60)

Phase			Secondary Follow-up												
Visit Name	Category	Protocol Section	Post-infusion											End of Secondary Follow-up	Survival Follow-up after study completion
Study day			M2 ±14d	M3 ±14d	M6 ±30d	M9 ±30d	M12 ±30d	M18 ±60d	M24 ±60d	M30 ±60d	M36 ±60d	M42 ±60d	M48 ±60d	M54 ±60d	M60 ±60d	q 3m
Concomitant medications (selected)	D	6.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	
Antineoplastic therapies after CTL019 infusion	D	7.1.5	X	X	X	X	X	X	X	X	X	X	X	X	X	
IWRS/IRT Registration	S														X	
Physical examination	S	7.2.2.1	X	X	X		X		X		X		X		X	
Performance status	D	7.2.2.4	X	X	X		X		X		X		X		X	
Weight	D	7.2.2.3	X	X	X		X		X		X		X		X	
Vital signs	D	7.2.2.2	X	X	X		X		X		X		X		X	
Efficacy assessments																
Current status of primary malignancy (only until patient progresses)	D	7.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety assessments																
Protocol defined Adverse events and AEs of special interest, including new malignancies	D	8.1 8.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancies	D	7.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum or Urine Pregnancy Test	S	7.2.2.5								X	X	X	X	X	X (Serum)	
Hematology (CBC & differential)	D	7.2.2.5	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Phase	Category	Protocol Section	Secondary Follow-up													
Visit Name			Post-infusion												End of Secondary Follow-up	Survival Follow-up after study completion
Study day			M2 ±14d	M3 ±14d	M6 ±30d	M9 ±30d	M12 ±30d	M18 ±60d	M24 ±60d	M30 ±60d	M36 ±60d	M42 ±60d	M48 ±60d	M54 ±60d	M60 ±60d	q 3m
Serum (immunogenicity, cytokines, etc.)	D	7.2.3 7.2.4		X	X		X									
CTL019 transgene persistence	D	7.2.2.5	X	X	X	X	X	X	X	X	X	X	X	X	X	
Peripheral blood (B and T cell levels in blood by flow cytometry)	D	7.2.2.5		X	X		X		X		X		X		X	
RCL by VSV-g q-PCR	D	7.2.2.5	X	X	X		X		X		X		X		X	
Survival follow-up	D	7.1.5	For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, whichever comes first. If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact													X
End of phase disposition	D	n/a													X	

[redacted]

7.1.1 Screening phase

After informed consent/assent is obtained, blood tests and assessments to determine eligibility as outlined below are performed.

Patients who have signed an informed consent/assent will be registered in the IRT system and undergo a routine lymphoma staging workup including:

a. Demography
b. Medical history and prior/concomitant medications and antineoplastic therapies
c. Tumor biopsy. A FFPE tumor sample obtained for the purpose of this study must be submitted, however if not clinically feasible, an archival tumor biopsy at most recent relapse may be submitted instead. Excisional biopsies should be submitted wherever possible; in cases where this is not possible, a core needle biopsy is allowable. Fine needle aspiration (FNA) is not allowed. If possible, an additional fresh frozen biopsy sample should be obtained for exploratory analysis.
d. Central pathology assessment of tumor biopsy
   - subtype determination
   - [redacted]
e. Physical Examination (PE) including height, weight, vital signs, extramedullary disease assessment and CNS symptom assessment
f. Performance status (ECOG)
g. Pulse oximetry
h. MUGA or ECHO
i. ECG
j. B-symptom assessment
k. Imaging (CT/MRI). Local assessment will be used to determine eligibility
l. Bone marrow biopsy and/or aspirate
m. CSF cytology
n. CNS Brain Imaging (MRI/CT) (if clinically indicated)
o. Hematology
p. Chemistry Panel
q. Serum pregnancy test (if female of childbearing potential)
r. Viral serology (CMV, EBV, HIV, HbsAg, HBsAb, HBcAb, HCV RNA). If HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines (see Appendix 2 for interpretation of Hepatitis B results)
s. Coagulation panel
t. Serum immunoglobulin levels (IgG, IgA, IgM)
u. Flow cytometry
v. Urinalysis

[redacted]

x. Adverse events

[redacted]

The below assessments do not need to be repeated if performed in the context of the leukapheresis protocol [CCTL019B2206] or if performed as part of clinical routine within 4 weeks of the signature of the CCTL019C2201 ICF:

a. Central flow cytometry
b. Serum immunoglobulin levels (IgG, IgA, IgM)
c. Viral serology (CMV, EBV, HIV, HbsAg, HBsAb, HBcAb, HCV RNA). If HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines (see Appendix 2 for interpretation of Hepatitis B results)

[redacted]

7.1.1.1 Criteria for repeating screening procedures prior to CTL019 infusion

In the event that the time between screening assessment and the enrollment exceeds 8 weeks the following must be repeated: ECHO/MUGA, ECG, performance status assessment, Complete Blood Count with differential and Platelet Count, Chemistry Panel, Coagulation Panel, Urinalysis, Serum Pregnancy test.

In the event that the time between screening assessment and enrollment exceeds 12 weeks, the below screening procedures must be repeated in addition to the above:

a. Physical Examination (PE) including height, weight, vital signs, extramedullary disease assessment and CNS symptom assessment
b. Pulse oximetry
c. Imaging (PET-CT or FDG-PET+CT/MRI)
d. Bone marrow biopsy and/or aspirate only if suspected or known bone marrow involvement
e. CSF cytology only if suspicion of CNS involvement
f. CNS Brain Imaging (MRI/CT) (if clinically indicated)

7.1.1.2 Eligibility screening and enrollment

For detailed enrollment procedures, including use of Interactive Response Technology (IRT), please refer to the IRT User Manual.

Only following informed consent to study CCTLC2201 information on the patient's apheresis product will be transferred to Novartis manufacturing. Novartis manufacturing will then evaluate the patient's apheresis product for acceptance. For sites performing the leukapheresis as part of this protocol leukapheresis can only be performed after patient consent has been obtained.

Enrollment is defined as the point at which a patient meets all clinical inclusion/exclusion criteria and the patient's apheresis product is accepted for manufacturing. The patient is then enrolled using the same Subject No. assigned at screening by the site investigator or designated staff. Once assigned, the Subject No. must not be reused for any other patient and the Subject No. for that individual must not be changed. If a screened patient is not enrolled for any reason, the specific reason will be entered into the clinical database.

[redacted]

IRT will continuously monitor the enrollment of different molecular DLBCL subtypes to ensure that a minimum of 25 patients are treated in each of the GC and ABC subtypes.

IRT Registration: To document screening and enrollment into the study, the IRT will be contacted initially after informed consent/assent is obtained and again after eligibility is confirmed. Furthermore infusion of CTL019 must be confirmed in the IRT system within 24 hours of infusion.

7.1.1.3 Information to be collected on patients not enrolled

The reason for not being enrolled will be entered in the clinical database. The demographic information, informed consent, Inclusion/Exclusion pages and any adverse events leading to subject discontinuation must also be completed for patients not enrolled. No other data will be entered into the clinical database for patients who are not enrolled.

7.1.2 Pre-treatment phase

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

Enrollment/Pre-chemotherapy evaluation visit (W-3 to D-8)

Prior to start of lymphodepleting therapy (the day before or on the day of the scheduled lymphodepleting chemotherapy regimen is to begin) the patient will undergo blood collection for safety [redacted] ssessments [redacted], humoral & cellular immunogenicity and RCL by VSV-G qPCR. In addition, adverse events and prior/concomitant medications will be reviewed. Viably frozen samples from the apheresis material as well as the CTL019 product will be collected at the manufacturing site for correlative studies.

Lymphodepleting chemotherapy visit (-D 14 to D-5) It is anticipated that many patients will have been receiving chemotherapy for relapse or resistant disease. Prior to CTL019 cell infusion and after apheresis, one cycle of lymphodepleting therapy is planned, if patients are not already lymphopenic. The use of additional chemotherapy prior to the recommended preinfusion lymphodepleting therapy will be at the discretion of the investigator and dependent on the patient's disease burden. If patients have a White Blood Cell (WBC) count ≤1,000 cells/μL within one week prior to CTL019 infusion, lymphodepleting chemotherapy is **NOT** required, however a visit should still occur during this time window, and required assessments should be completed.

At this visit patients will undergo blood test for hematology and chemistry, a pregnancy test (all female patients of childbearing potential), rapid influenza testing and in addition, the patients weight, adverse events and prior/concomitant medications will be reviewed. For patients who do receive lymphodepleting therapy, this visit should occur within 24 hours of starting lymphodepleting chemotherapy.

Lymphodepleting therapy should be started 14 to 5 days before CTL019 infusion (D1) to allow for at least 48 hours from last dose of lympodepleting therapy to CTL019 infusion. The purpose of the lymphodepleting therapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CTL019 cells. Fludarabine (25 mg/m^2 i.v. daily for 3 doses) and cyclophosphamide (250 mg/m^2 i.v. daily for 3 doses starting with the first dose of fludarabine)

[redacted]

is the regimen of choice, as there is the most experience with the use of this regimen in facilitating adoptive immunotherapy. Refer to Section 2.2.1 for additional information regarding lymphodepleting chemotherapy.

Note: All patients must undergo a rapid influenza diagnostic test within 10 days prior to the planned CLT019 infusion. If the patient is positive for influenza, oseltamivir phosphate or zanamivir should administered for 10 days as preventative treatment (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their 10 day preventative treatment course prior to receiving CTL019. The test does not need to be repeated prior to CTL019 infusion however if influenza signs and symptoms are present, CTL019 infusion should be delayed until the patient is asymptomatic.

For patients residing in the United States, Canada, Europe and Japan, influenza testing is required during the months of October through May (inclusive). For patients residing in the southern hemisphere such as Australia, influenza testing is required during the months of April through November (inclusive). For patients with significant international travel, both calendar intervals above may need to be considered.

A PET-CT (or CT/MRI and dedicated FDG PET when PET-CT not available) must be performed within four weeks prior to scheduled infusion of the CTL019 product, and should be scheduled as close to CTL019 infusion as possible. This imaging assessment will form the baseline for all subsequent efficacy evaluations. B-symptoms will also be evaluated at that time.

Pre-infusion visit (D-1)

On the day prior to the scheduled CTL019 infusion, patients will undergo a physical exam (including vital signs), a performance status assessment, blood collection for safety [redacted] assessments and humoral & cellular immunogenicity. In addition, adverse events and prior/concomitant medications will be reviewed.

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

7.1.3 Treatment and primary follow-up phase

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

Infusion visit (D1)

Infusions will begin 2 to14 days after completion of lymphodepleting chemotherapy.

The day of (but prior to) the CTL019 infusion, patients will undergo a physical examination including weight, a performance status assessment, pulse oximetry, ECG, and blood tests including chemistry, a CBC with differential, and coagulation panel. Final CTL019 infusion pre-requisites (including an ECG and a rapid influenza test) will be checked prior to infusion (per Section 6.1.1.2).

CTL019 transduced T cells will be given as a single dose with a target of 5×10^8 CTL019 transduced cells. Vital signs will be monitored before and following CTL019 infusion (per Section 6.1.1.2). An additional blood sample will be collected post-infusion for CTL019 PK assessment. In addition, adverse events and prior/concomitant medications will be reviewed.

Details on the administration of the CTL019 infusion are found in Section 6.1.1.2.

[redacted]

For all patients who receive a CTL019 infusion, additional follow-up will be made to determine survival every 3 months. If a patient misses a quarterly scheduled visit where survival status is required, or if the quarterly time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact, and the survival eCRF must be entered.

Post-infusion visits: D2, D4±1d, D7±1d, D11±1d, D14±1d, D17±1d, D21±3d

At the intervals following infusion listed above, patients will undergo one or more of the following: blood tests including chemistry, hematology, coagulation, serum immunoglobulin, humoral & cellular immunogenicity, [redacted] flow cytometry (b cells, [redacted] and CD19 assessment), a physical exam (with vital signs), performance status assessment and pulse oximetry. In addition, adverse events and prior/concomitant medications will be reviewed.

Weekly sample collections for serum cytokines, CTL019 PK, [redacted] are mandated during the first 28 days following CTL019 infusion. However, as the time-course and rapidity of CRS development varies among patients, additional unscheduled samples for these markers may also be collected as needed, if it is clinically feasible. [redacted]

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

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

Post-infusion visit (D28 ±7d)

Patients will undergo blood collection for hematology, chemistry, coagulation, serum immunoglobulins, cytokines, flow cytometry (B cells, [redacted] and CD19 assessment) humoral and cellular immunogenicity, and CTL019 PK, [redacted] Patients will also have their B-symptoms assessed, Imaging (CT/MRI) assessments performed, a physical examination (including vital signs, weight) and a performance status assessment. If at this visit the patient has a radiological CR based upon imaging assessments, a bone marrow biopsy needs to be performed in patients that had prior bone marrow involvement to confirm the CR. Due to the mechanism of action of CTL019, the Day 28 assessment should be interpreted in context of other clinical parameters that suggest true progression rather than pseudo-progression due to inflammatory changes and tumor swelling (De Velasco et al 2015). Adverse events and prior/concomitant medications will be reviewed.

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

[redacted]

Post-infusion visits M2±14d, M3±14d, M4±14d, M5±14d, M6±14d

At the intervals following infusion listed above, patients will undergo one or more of the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B cells, [redacted] and CD19 assessment), cytokines, humoral & cellular immunogenicity and CTL019 PK, [redacted] and RCL by VSV-G qPCR. In addition, at the intervals following infusion listed above patients will undergo one or more of the following: a physical exam (including vital signs and weight), a performance status assessment, B-symptom assessment, Imaging (CT/MRI) assessment, PET-CT (or dedicated FDG PET when PET-CT not available) (Month 3 only) a bone marrow biopsy and/or aspirate (Month 3 only), [redacted] Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

For details of assessments required at each specific visit, refer to Table 7-1.

Post-infusion visit M9 ±14d

Patients will undergo one or more of the following: blood collection for hematology, chemistry, serum immunoglobulins and CTL019 PK. In addition, patients will undergo a physical exam (including vital signs and weight), performance status assessment, B-symptom assessment, Imaging (CT/MRI) assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

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

Post-infusion visit M12 ±14d

Patients will undergo the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B cells, [redacted] and CD19 assessment), cytokines, humoral & cellular immunogenicity and CTL019 PK, [redacted] RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including vital signs and weight), a performance status assessment, B-symptom assessment, Imaging (CT/MRI) assessment, [redacted]. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

Patients with CD19 CART transgene levels equal to or greater than 1% of WBC

If ≥ 1% of the WBC in peripheral blood are positive for CD19 CAR vector sequences by qPCR at > 12 months from CD19 CART infusion, then the patient will be asked to return for a confirmatory blood test prior to the next 6 month visit. If ≥1% of the WBC is positive upon the receipt of the confirmatory qPCR result, then the genomic vector integration sites will be determined. Identified vector integration sites will be evaluated using bioinformatic approaches to determine the frequency of integration events in regions with known relationships to human cancers (i.e. near oncogenes). If integration site analysis reveals mono- or oligo-clonality pattern and/or integration at or near an oncogenic locus, a monitoring plan, including follow-up molecular analyses, will be developed in collaboration between the Investigator, Sponsor [redacted]

and Health Authorities that is specific for the health care risks that are anticipated given the nature of the integration site and vector target cell type.

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

Post-infusion visit M18 ±14d and M24 ±14d

At the intervals following infusion listed above, patients will undergo one or more of the following: blood collection for hematology, chemistry, flow cytometry (B cells, [redacted] and CD19 assessment), cytokines, humoral & cellular immunogenicity and CTL019 PK, [redacted], and RCL by VSV-G qPCR (Month 24 only). In addition, at the intervals following infusion listed above patients will undergo one or more of the following: a physical exam (including vital signs and weight), a performance status assessment, B-symptom assessment, Imaging (CT/MRI) assessment [redacted]. Protocol defined adverse events, adverse events of special interest (including new malignancies) and selected concomitant medications will be reviewed. Any pregnancies will be reported.

For details of assessments required at each specific visit, refer to Table 7-1.

Post-infusion visits M30 ±14d, M42 ±14d, M54 ±14d

At the intervals following infusion listed above, patients will undergo one or more of the following: blood collection for hematology, chemistry, flow cytometry. In addition, at the intervals following infusion listed above patients will undergo one or more of the following: a physical exam (including vital signs and weight), a performance status assessment and B-symptom assessment. Protocol defined adverse events, adverse events of special interest (including new malignancies) and selected concomitant medications will be reviewed. Serum or urine pregnancy test will be done for WOCBP until contraception is no longer required. Any pregnancies will be reported.

For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, [CCTL019A2205B], whichever comes first, is required. If a patient misses a quarterly scheduled visit where survival status is required, or if the quarterly time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact.

For details of assessments required at each specific visit, refer to Table 7-1.

Post-infusion visits M36 ±14d and M48 ±14d

At the intervals following infusion listed above, patients will undergo one or more of the following: blood collection for hematology, chemistry, flow cytometry (B cells, [redacted] and CD19 assessment), cytokines, humoral & cellular immunogenicity and CTL019 PK, [redacted], and RCL by VSV-G qPCR. In addition, at the intervals following infusion listed above patients will undergo one or more of the following: a physical exam (including vital signs and weight), a performance status assessment, B-symptom assessment, Imaging (CT/MRI) assessment [redacted]. Protocol defined adverse events, adverse events of special interest (including new malignancies) and selected concomitant medications will be reviewed. Serum or urine

[redacted]

pregnancy test will be done for WOCBP until contraception is no longer required. Any pregnancies will be reported.

For details of assessments required at each specific visit, refer to Table 7-1.

7.1.3.1 End of treatment and primary follow-up (EOT) visit (M60 ±14d) including premature withdrawal

The End of Treatment and Primary Follow-Up (EOT) visit for each patient will be 60 months (5 years) from the date of their infusion if they complete all scheduled visits. If a patient discontinues early from the primary follow-up, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the Month 60 visit will be performed. An End of Treatment and Primary Follow-Up Disposition Case Report/ Record Form (CRF) page should be completed, giving the date and reason for stopping the treatment and primary follow-up phase.

During the End of Treatment and Primary Follow-Up visit, patients will undergo the following: blood collection for hematology, chemistry, serum immunoglobulins, CTL019 PK, [redacted] flow cytometry (B cells, [redacted]), cytokines and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including vital signs and weight), performance status assessment, B-symptom assessment, Imaging (CT/MRI) assessment, [redacted]. Protocol defined adverse events, adverse events of special interest (including new malignancies) and selected concomitant medications will be reviewed. A Serum pregnancy test will be done for WOCBP until contraception is no longer required. Any pregnancies will be reported.

Following completion of the Treatment and Primary Follow-Up, patients will be followed for survival until the end of the study as defined in Section 4.2 (Section 7.1.5) or patients will be enrolled in the long term follow-up (LTFU) study, whichever occurs first. Patients who discontinue or withdraw from the Treatment and Primary Follow-Up early for any reason will be asked to continue the study in the Secondary Follow-up Phase through Month 60.

7.1.3.2 Criteria for premature patient withdrawal from treatment and primary follow-up phase

Patients must be followed according to the visit schedule for the Treatment and Primary Follow-Up to ensure adequate data are collected for the proper assessment of study primary and secondary objectives. Patients may voluntarily withdraw from the Treatment and Primary Follow-Up Phase or be dropped from it at the discretion of the investigator at any time. It is anticipated that patients may leave the primary follow-up and move to Secondary Follow-Up due to reasons including:

- Disease progression/Relapse after remission,
- Pursuing HSCT while in remission, or
- Patient voluntary withdrawal from the primary follow-up.

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show “due diligence” by

[redacted]

documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.1.4 Secondary follow-up phase

Patients who discontinue the Treatment and Primary Follow-Up Phase before month 60 will continue to be followed in the secondary follow-up phase in order to collect health authority requested data (e.g. protocol defined adverse events) up to 5 years after CTL019 infusion.

The first visit in the Secondary Follow-Up Phase is determined according to the time since CTL019 infusion when the patient discontinued from the Treatment and Primary Follow-Up Phase. For example, if the patient discontinues from the Treatment and Primary Follow-Up phase at Month 10, the first visit in the Secondary Follow-Up Phase will be Month 12.

For details of assessments, refer to Table 7-2. During the secondary follow-up phase, patients will undergo one or more of the following at each visit according to Table 7-2: Blood collection for hematology, serum immunoglobulins, humoral immunogenicity, cytokines, CTL019 PK, flow cytometry (B cells, [redacted]) and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including weight), vital signs, and a performance status assessment. Protocol defined adverse events, adverse events of special interest (including new malignancies) and selected prior/concomitant medications will be reviewed. Serum or urine pregnancy test will be done between M30 and M54, and a serum pregnancy test at M60 for WOCBP until contraception is no longer required. Any pregnancies will be reported. Efficacy will be assessed until patient progresses. For these patients, relapse status of primary malignancy will be assessed at each visit.

In the event a patient cannot attend any visit during the secondary follow-up, the investigator should attempt to contact the patient by phone to determine, at a minimum, primary malignancy status and survival status.

For details of assessments, refer to Table 7-2.

Additional follow-up will be made to determine survival status for patients every 3 months. If a patient misses a quarterly scheduled visit where survival status is required, or if the quarterly time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact, and the survival eCRF must be entered.

7.1.4.1 Criteria for premature patient withdrawal from the study

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show “due diligence” by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

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

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

[redacted]

d. Termination of the study by the sponsor or the health authorities

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

7.1.5 Survival follow-up phase

For all patients who complete the primary follow-up or prematurely discontinue from the primary or secondary follow-up phase, every attempt should be made to follow the patients to determine survival every 3 months post-CTL019 infusion until the end of study as defined in Section 4.2, or until the patient is enrolled in the long term follow-up (LTFU), whichever occurs first. Survival status can be obtained via phone contact with the patient.

7.1.6 Long-term follow-up

As a single administration study, patients are followed on study for 5 years post-infusion for safety and efficacy evaluations. A long term post-study follow-up for lentiviral vector safety will continue under a separate destination protocol. Patients will continue to be followed until 15 years post-CTL019 infusion per health authority guidelines.

Under the long term follow-up protocol, 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 automatically enrolled in this destination protocol at the time of study completion/discontinuation (separate informed consent/assent forms will be provided for this protocol). One to two times a year patients will visit the clinical site for a physical exam and medical history (including concomitant medications and adverse events) with careful attention to features possibly related to lentiviral associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, or new incidence of other hematologic disorders. In addition, labs will be drawn to evaluate routine safety endpoints, CTL019 vector persistence and RCL.

7.1.7 Discontinuation of study treatment

Not applicable as patient will only receive 1 dose of CTL019 at Day 1

7.1.8 Withdrawal of consent

Patients may voluntary withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

[redacted]

7.1.9 Follow up for safety evaluations

Please refer to Section 7.1.4 and Section 7.1.6.

7.1.10 Lost to follow-up

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

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments will be performed as indicated in Table 7-1, and as clinically indicated until relapse or progression. Efficacy evaluation will be based on recommendations by the International Malignant Lymphomas Imaging Working Group (Cheson et al 2014; Barrington et al 2014) and detailed as an appendix to the protocol (Guideline for Efficacy Evaluation in DLBCL and FL studies, version 2).

An Independent Review Committee (IRC) appointed by Novartis will review data related to disease response assessment according to the Guideline for Efficacy Evaluation in DLBCL and FL studies, version 2. Radiological imaging will be transmitted by the sites to the imaging Contract Research Organization (CRO) designated by Novartis to undergo quality checks and central review by the IRC. Clinical data such as, physical exam, bone marrow results, B-symptoms, pathology/histology and cytology results; as well as, information regarding prior interventions, pre-existing radiographic findings that may mimic metastatic disease at baseline/screening and on-study interventions will be transmitted to the imaging CRO for review by a medical oncologist/hematologist. Further details regarding the IRC assessment will be provided in the IRC charter. The central review of the scans will be carried out in a blinded fashion. The decision regarding patient management will remain with the local investigator. Enrollment eligibility will be determined by the local staging assessment of the required images obtained during screening. Imaging studies used to determine eligibility must be submitted to the IRC.

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

- Central pathology assessment
- Molecular subtype determination by central laboratory
- Imaging
- Bone marrow biopsy or aspirate

[redacted]

- CSF cytology
- B-symptoms
- Physical exam

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The results of the central evaluations will be used for primary analysis purposes. The local investigator's assessment will be used for treatment decision making. Any imaging assessments already completed during the regular work-up of the patient within 8 weeks prior to start of screening , including before signing the main study ICF, can be considered as the screening images for this study. Any imaging assessments obtained after infusion cannot be considered baseline images.

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

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

A PET-CT (or CT/MRI and FDG PET when PET-CT not available) must be performed within four weeks prior to scheduled infusion of the CTL019 product, and should be scheduled as closely as possible to CTL019 infusion and at Month 3. The CT component of the PET-CT may be used in lieu of a standalone CT/MRI, only if the CT component is of similar diagnostic quality as a contrast enhanced CT performed without PET. If contrast enhanced PET-CT is not available, a standard FDG-PET must be performed and a standalone diagnostic CT/MRI should be performed in addition to the FDG-PET scan. If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast as to not compromise PET results. The PET-CT acquisition methodology (e.g., administration of intravenous contrast) should remain consistent between baseline and Month 3 for any given patient.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment. It is recommended to verify disease progression by PET-CT.

[redacted]

Table 7-3 Imaging or disease assessment collection plan

Procedure	Screening/Pre-infusion	Post-infusion Assessment
PET-CT with contrast enhanced CT	Mandated within 4 weeks prior to scheduled infusion of CTL019 product	Mandated at Month 3
Dedicated FDG PET	Mandated if no PET-CT available within 4 weeks prior to scheduled infusion of CTL019 product	Mandated at Month 3 if no PET CT available
CT/MRI (Chest, Abdomen, Pelvis, Neck)	Mandated to determine study eligibility Mandated within 4 weeks prior to scheduled infusion of CTL019 product if no PET-CT available or if the CT component of the PET-CT scan is not of diagnostic quality	Mandated at Day 28, Months 6, 9, 12, 18, 24, 36, 48 and 60 and as clinically indicated Mandated at Month 3 if no PET-CT available Due to the mechanism of action of CTL019, the Day 28 assessment should be interpreted in context of other clinical parameters that suggest true progression rather than pseudoprogression due to inflammatory changes and tumor swelling.
CNS Imaging (CT/MRI)	As clinically indicated	As clinically indicated
Bone marrow aspirate and biopsy DLBCL cells	Mandated	Mandated at time of radiological CR in patients with baseline bone marrow disease and as clinically indicated Mandated at Month 3 in all patients
Tumor biopsy (FFPE) for central pathology assessment and DLBCL subtype determination	Mandated	n/a
[redacted]		
CSF Cytology	Mandated	As clinically indicated

The status of primary malignancy based on clinical routine assessments will be recorded for patients with ongoing response during follow up. The CD19 status at time of relapse should be recorded.

7.2.2 Safety and tolerability assessments

For patients in the primary follow-up, safety will be monitored by assessing immunogenicity against CTL019, lab abnormalities, physical examination, ECG, and vital signs, as well as collecting adverse events continuously until Month 12. After Month 12 only selected AEs (protocol defined AEs) will be collected.

For patients in the secondary follow-up, only selected AEs (protocol defined) will be collected.

For complete details on AE collection, reporting and adverse events of special interest, refer to Section 8.

For all patients either in the primary or the secondary follow-up, any pregnancies will need to be reported and followed-up.

[redacted]

7.2.2.1 Physical Examination

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

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

7.2.2.2 Vital Signs

Vital signs include temperature, blood pressure, pulse, respiratory rate, and pulse oximetry. Pulse oximetry will be performed only at Screening, Day 1 (prior to infusion) through Day 14. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

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

7.2.2.3 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 according to Table 7-1.

7.2.2.4 Performance status

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

Table 7-4 ECOG Performance status grade

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[redacted]

7.2.2.5 Laboratory evaluations

Laboratory assessments will be performed according to Table 7-1 and Table 7-2. Note: Additional assessments should be performed between visits as clinically indicated and to follow AEs or CTL019 expected events. For all laboratory assessments that occur on Day 1, these should be performed prior to CTL019 infusion unless indicated otherwise.

Table 7-5 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCHC, MCV, Platelets, Red blood cells, White blood cells with complete differential (Basophils, Eosinophils, Lymphocytes, Atypical Lymphocytes, Monocytes, Neutrophils , Lymphoblasts, Plasma cells, Prolymphocytes, Myelocytes, Metamyelocytes, and Promyelocytes)
Chemistry	Glucose, Blood Urea Nitrogen (BUN), Creatinine, eGFR, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Magnesium, Phosphorus, LDH, [redacted] and Uric Acid
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity) If macroscopic panel is abnormal then perform microscopic panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR), activated Partial thromboplastin time (aPTT), fibrinogen, and D-dimer
Pregnancy screen for WOCBP	Serum and urine pregnancy test is required as long as contraception is required. Refer to Table 7-1 and Table 7-2 for the timepoints.
Influenza	Rapid Influenza A & B Test
Viral Serology	Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Hepatitis C Virus RNA, Hepatitis B surface antigen (HbsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), HIV test (if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines)
Additional assessments	Serum immunoglobulin levels (IgG, IgA, IgM)

CTL019 PK will be quantified by q-PCR and flow cytometry in peripheral blood and bone marrow. [redacted] Replication competent lentivirus (RCL) will be detected by q-PCR for VSV-G in peripheral blood. See Table 7-6. If negative after the first year, samples will be collected and stored but not analyzed unless requested for safety purposes.

Table 7-6 Central clinical laboratory parameters collection plan

Test Category	Test Name/Method
CD19 testing	Immunohistochemistry or flow cytometry
DLBCL and subtype determination	Immunohistochemistry
[redacted]	
Bone marrow aspirate/biopsy	Flow cytometry or immunohistochemistry

[redacted]

Test Category	Test Name/Method
[redacted]	
RCL (VSV-G)	VSV-g q-PCR (whole blood)
Cytokines	Serum cytokine panel, PD1, PDL1 (peripheral blood, CSF)
Immunogenicity	Incidence and prevalence (pre-existing) of immunogenicity against CTL019 (peripheral blood and serum)
CTL019 pharmacokinetics	CTL019 PK by q-PCR or flow cytometry (peripheral blood, bone marrow aspirate)
[redacted]	
Additional assessments	Serum immunoglobulin levels (IgG, IgA, IgM) (Secondary follow-up only) [redacted]

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

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at:

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

The date and time of the ECG and the following parameters will be collected and assessed: QTcF, PR, QT and QRS interval in msec, heart rate (bpm).

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.2.6.2 Cardiac imaging – MUGA (multiple gated acquisition) scan or echocardiogram (ECHO)

An ECHO/MUGA test is required to be completed at screening. Clinically significant abnormalities present when the patient signed the informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. Patients must have a left ventricular ejection fraction (LVEF) $\geq$ 45% to be included into the study.

[redacted]

7.2.3 Cellular Kinetics and Pharmacokinetics

Blood and BM sampling for PK evaluations will be performed at specified time-points. All collections of PK blood samples will be recorded on the appropriate PK blood collection CRF page. Refer to the [Laboratory Manual] for details on sample handling and shipment.

Table 7-7 CTL019 pharmacokinetics by q-PCR in peripheral blood collection log

Cycle	Day*	Scheduled time point relative to dosing	PK DRID (CTL019)*	PK Sample No. (CTL019)	Blood Volume (mL)
1	W-3 to D-8 Enrollment/Pre-Chemotherapy	Pre-dose	201	201	6
1	D1 10 minutes ± 5 minutes post-infusion	0.167h post-dose (±5 min)	201	202	6
1	D2	24h (+/-6h)/D2	201	203	6
1	D4±1d	72hD4	201	204	6
1	D7±1d	D7	201	205	6
1	D11±1d	D11	201	206	6
1	D14±1d	D14	201	207	6
1	D17±1d	D17	201	208	6
1	D21±3d	D21	201	209	6
1	D28±7d	D28	201	210	6
1	M2±14d	M2	201	211	6
1	M3±14d	M3	201	212	6
1	M6±14d	M6	201	213	6
1	M9±14d	M9	201	214	6
1	M12±14d	M12	201	215	6
1	M18±14d	M18	201	216	6
1	M24±14d	M24	201	217	6
1	M30±14d	M30	201	218	6
1	M36±14d	M36	201	219	6
1	M42±14d	M42	201	220	6
1	M48±14d	M48	201	221	6
1	M54±14d	M54	201	222	6
1	M60±14d	M60	201	223	6
1	Unscheduled PK samples related to CRS[a]		201	2001	6
1	Unscheduled (PK samples related to safety events, relapse) [b]		201	3001	6
1	Unscheduled (PK samples at relapse)[c]		201	6001	6

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.
**Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible. See Section 7.1.3

[redacted]

Cycle	Day*	Scheduled time point relative to dosing	PK DRID (CTL019)*	PK Sample No. (CTL019)	Blood Volume (mL)
[redacted]					

[b]Unscheduled PK samples related to other non-CRS safety events are uniquely, sequentially numbered 3001, 3002, etc.

[c]In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-12 and Table 7-13)

Note: If RCL testing was negative through Month 12, all samples taken after Month 12 will be stored for potential future testing.

Table 7-8 CTL019 pharmacokinetics by flow cytometry in peripheral blood collection log

Cycle	Day*	Scheduled time point relative to dosing	PK DRID (CTL019)*	PK Sample No. (CTL019)	Blood Volume (mL)
1	W-3 to D-8 Enrollment/Pre-chemotherapy evaluation	Pre-dose	201	301	2
1	D1 10 minutes ± 5 minutes post-infusion	0.167h post-dose (±5 min)	201	302	2
1	D4±1d	72hD4	201	303	2
1	D7±1d	D7	201	304	2
1	D11±1d	D11	201	305	2
1	D14±3d	D14	201	306	2
1	D17±1d	D17	201	307	2
1	D21±3d	D21	201	308	2
1	D28±7d	D28	201	309	2
1	M2±14d	M2	20 1	310	2
1	M3±14d	M3	201	311	2
1	M6±14d	M6	201	312	2
1	M9±14d	M9	201	313	2
1	M12±14d (EOT)	M12	201	314	2
1	M18±14d	M18	201	315	2
1	M60±14d	M60	201	316	2
1	Unscheduled PK samples related to CRS[a]		201	4001	2
1	Unscheduled (PK samples related to safety events, relapse) [b]		201	5001	2
1	Unscheduled (PK samples at relapse)[c]		201	7001	2

[redacted]

Cycle	Day*	Scheduled time point relative to dosing	PK DRID (CTL019)*	PK Sample No. (CTL019)	Blood Volume (mL)
*All measurement times are relative to date of CTL019 infusion unless otherwise specified. **Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible. See Section 7.1.3 [redacted] [b]Unscheduled anytime PK samples related to other non-CRS safety events will be uniquely, sequentially numbered 5001, 5002, etc. [c]In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-12 and Table 7-13)					

Table 7-9 CTL019 pharmacokinetics by q-PCR in bone marrow aspirate collection log

To be completed only if bone marrow examined

Cycle	Day*	Scheduled time point relative to dosing	PK DRID (CTL019)*	PK Sample No. (CTL019)	Sample Volume (mL)
1	W-8 to W-4 Screening	Pre-dose/screening	201	401	2
1	M3±14d	M3	201	402	2
1	Unscheduled (e.g. at time of radiological CR, related to relapse) [a]		201	403	2
*All measurement times are relative to date of CTL019 infusion unless otherwise specified. a.Unscheduled time points begin with 403, 404, 405 series					

Table 7-10 CTL019 pharmacokinetics by flow cytometry in bone marrow aspirate collection log

To be completed only if bone marrow examined

Cycle	Day*	Scheduled time point relative to dosing	PK DRID (CTL019)*	PK Sample No. (CTL019)	Sample Volume (mL)
1	W-8 to W-4 Screening	Pre-dose/screening	201	501	2
1	M3±14d	M3	201	502	2
1	Unscheduled (e.g. at time of radiological CR, related to relapse) [a]		201	503	2
*All measurement times are relative to date of CTL019 infusion unless otherwise specified. a.Unscheduled time points begin with 503, 504, 505 series"					

[redacted]

Table 7-11 CTL019 pharmacokinetics by q-PCR in CSF biopsy or other tissue log

To be completed only if CSF collection performed.

Day/ Scheduled Time Point*	Sample Volume
W-8 to W-4 Screening	4-8 mL
Unscheduled (e.g. related to relapse)	4-8 mL

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.

Table 7-12 Immunogenicity serum sample collection log

Day/ Scheduled Time Point*	Sample volume
W-3 to D-8 Enrollment/Pre-chemotherapy evaluation	**
D14±1d	**
D28±7d	**
M3±14d	**
M6±14d	**
M12±14d	**
Unscheduled (at relapse)***	**
Unscheduled (e.g. related to safety events)	**

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.
** Aliquots are derived from the serum cytokine collections; refer to Table 7-17.
***In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK sample (refer to Table 7-7, Table 7-8)

Table 7-13 Immunogenicity whole blood sample collection log

Day/ Scheduled Time Point	Sample volume
W-3 to D-8 Enrollment/Pre-chemotherapy evaluation	**
D14±1d	**
D28±7d	**
M3±14d	**
M6±14d	**
M12±14d	**
Unscheduled (at relapse)***	
Unscheduled (e.g. related to safety events)	**

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.
[redacted]
***In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK sample (refer to Table 7-7, Table 7-8)

[redacted]

Table 7-14 [redacted] CTL019 Pharmacokinetics (PK), [redacted] treated patients during CRS

Day/ Scheduled Time Point*/**	[redacted] Dose Reference ID	[redacted] Sample Number	[redacted] Sample Volume (serum)	CTL019 Dose Reference ID	CTL019 PK by qPCR Sample Number^	Sample Volume (whole blood)	CTL019 PK by flow cytometry Sample Number^	Sample Volume (whole blood)
D1 (5-15 minutes post infusion)	101	1	5 mL	201	--	--	--	--
D1 1h ± 15 min post infusion	101	2	5 mL	201	251	2 mL	351	2 mL
D2 ± 2h	101	3	5 mL	201	252	2 mL	352	2 mL
D3 ± 4h	101	4	5 mL	201	253	2 mL	353	2 mL
D7 ± 1d	101	5	5 mL	201	254	2 mL	354	2 mL
D1 (pre-dose; second infusion)	101	6	5 mL	201	255	2 mL	355	2 mL
D1(5-15 minutes post second infusion)	102	7	5 mL	201	--	--	--	--
D2 ± 2h from second infusion	102	8	5 mL	201	256	2 mL	356	2 mL
D3 ± 4 hours (post second infusion)	102	9	5 mL	201	257	2 mL	357	2 mL
D7±1d (post second infusion)	102	10	5	201	258	2 mL	358	2 mL
D1 (5-15 minutes pre-dose; additional infusion)	102	11	5 mL	201	259	2 mL	359	2 mL
D1 (5- 15 minutes post additional infusion	103	12	5 mL	201	--	--	--	--
D2 ± 2 hours	103	13	5 mL	201	260	2 mL	360	2 mL
D3 ± 4 hours	103	14	5 mL	201	261	2 mL	361	2 mL
D7 ± 1d	103	15	5 mL	201	262	2 mL	362	2 mL
Additional***	104,105	16, 17, 18, 19, 20	5 mL	201	263, 264, 265, 266	2 mL	363, 364, 365, 366	2 mL

*All measurement times are relative to [redacted] infusion unless otherwise specified. A serum sample collected at D -1 for cytokine analysis (see Table 7-17 would serve as the baseline sample.
**Samples may be collected as needed dependent upon administration of [redacted] if clinically feasible.
Unscheduled CTL019 PK sample collections related to CRS as specified in Table 7-7 will cease once

[redacted]

Day/ Scheduled Time Point*/**	Toci Dose Reference ID	Toci Sample Number	Toci Sample Volume (serum) [redacted]	CTL019 Dose Reference ID	CTL019 PK by qPCR Sample Number^	Sample Volume (whole blood)	CTL019 PK by flow cytometry Sample Number^	Sample Volume (whole blood)
[redacted]								

^PK collections for CTL019 measured by qPCR will be numbered starting with 251 series and PK collections measured by flow cytometry will be numbered starting with a 351 series

[redacted]

Table 7-15 [redacted] CTL019 PK [redacted] treated patients during CRS

Day/ Scheduled Time Point*/**	Dose Reference ID	[redacted] Sample Number	Sample Volume (serum) [redacted]	CTL019 PK by qPCR Sample Number	Sample Volume (whole blood)	CTL019 PK by flow cytometry Sample Number	Sample Volume (whole blood)
D1 (5-15 minutes post infusion)	301	401	5 mL	--	--	--	--
D1 1 hour ± 15 min post infusion	301	402	5 mL	501	2 mL	701	2 mL
D2 ± 2 hours	301	403	5 mL	502	2 mL	702	2 mL
D3 ± 4 hours	301	404	5 mL	503	2 mL	703	2 mL
D7 ± 1d	301	405	5 mL	504	2 mL	704	2 mL
D1 (pre-dose; additional infusion)	301	406	5 mL	505	2 mL	705	2 mL
D1(5-15 minutes post additional infusion)	302	407	5 mL	--	--	--	--
D2 ± 2 hours from additional infusion	302	408	5 mL	506	2 mL	706	2 mL
D3 ± 4 hours	302	409	5 mL	507	2 mL	707	2 mL
D7 ± 1d	302	410	5 mL	508	2 mL	708	2 mL
Additional***	303, 304	411, 412, 413, 414, 415	5 mL	509, 510, 511, 512	2 mL	709,710, 711, 712	2 mL

*All measurement times are relative to [redacted] administration unless otherwise specified. A serum sample collected at D1 for cytokine analysis (see Table 7-17) would serve as the baseline sample.

**Samples may be collected as needed dependent upon administration o [redacted] if clinically feasible.

Unscheduled CTL019 PK sample collections related to CRS as specified in Table 7-7, Table 7-8, and will cease once PK/PD sample collections related to [redacted] administration commence, if applicable.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent/assent has been obtained.

Abnormal laboratory values or test results occurring after informed consent/assent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

8.1.2 Reporting

Adverse events that begin or worsen after informed consent/assent will be recorded in the patient's source documents. New or worsening adverse events **prior to starting study treatment** (i.e. lymphodepleting chemotherapy or the pre-infusion visit if the lymphodepleting chemotherapy is not given per Section 6.1.1.1) are required to be recorded in the Adverse Events CRF if they meet one of the following criteria:

- All infections
- All clinical AEs grade ≥ 3
- All laboratory abnormalities deemed clinically significant by the investigator
- All AEs related to a study procedure
- All AEs leading to study discontinuation
- All SAEs meeting criteria outlined in Section 8.2.2

Concomitant medications during the pre-screening period will also follow modified reporting criteria as described in Appendix 3.

Once the patient begins lymphodepleting chemotherapy or the pre-infusion visit, all new or worsening adverse events, including laboratory abnormalities deemed clinically significant by the investigator, regardless of causality will be recorded in the Adverse Events CRF up to the Month 12 visit.

Adverse event monitoring should be continued through the Month 60 (EOT) visit. **Following the Month 12 visit, and through the Month 60 visit**, adverse events should only be reported to Novartis and recorded in the Adverse Events CRF if it meets one of the following criteria:

- Events leading to death
- Events related to a study procedure
- Infections:
- Serious or opportunistic infections that fulfill one of the following criteria:

[redacted]

  - Require anti-infective treatment OR
  - Lead to significant disability or hospitalization OR
  - Need surgical or other intervention
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of other hematologic disorder
- Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy
- Positive RCL test result
- Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene
- New malignancy (T-cell & non T-cell), other than the primary malignancy
- Progressive multifocal leucoencephalopathy (PML)
- Hepatitis B reactivation

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

Adverse events will be assessed according to the Medical Dictionary for Regulatory Authorities (MedDRA) and the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, with the exception of CRS, which will follow Table 6-1. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent/assent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE v. 4.03 Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, temporarily interrupted, permanently discontinued, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event is defined as in Section 8.2.1

[redacted]

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, 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.

Modified data capture for inpatient/in hospital events

A significant number of CTL019 treated patients will require multiple days of inpatient and/or ICU care within 28 days after CTL019 infusion. These adverse events are mostly due to CRS and MAS, although there may be some contribution from the preceding lymphodepleting chemotherapy (neutropenia fever, cytopenias). CRS/MAS toxicity is an 'on-target' effect resulting from the expected CTL019 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 capture will be utilized for this study to systematically collect subsets of patient data to describe the management of safety events associated with CTL019 therapy for the purpose of:

1. Adequately informing physicians and patients of the expected risks of CTL019 and the recommended interventions to manage these risks
2. Health authority submission

This is done through a targeted collection of concomitant medications and laboratory data and CRS CRFs specifically designed to capture CTL019-related toxicity, severity, interventions and response/resolution following intervention. Details can be found in the CRF Completion Guidelines (CCGs) and Appendix 3 and 4.

8.1.3 Laboratory test abnormalities

8.1.3.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an adverse event should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be

[redacted]

reported as such. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin).

8.1.4 Adverse events of special interest

An adverse event of special interest (AESI, serious or non-serious) is one of greater scientific and medical concern specific to CTL019. The current defined AESIs for CTL019 include Cytokine Release Syndrome, Tumor Lysis Syndrome, Neutropenic fever, Cytopenia >28 days, drop in cardiac ejection fraction, neurotoxicity, hepatic events (Section 6.3), and infections.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event
- 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:

- Deaths beyond 30 days after CTL019 infusion, if there is a least a possible causality to CTL019
- Non-fatal disease progression should not be reported as AE.

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has begun study-related treatment (i.e. lymphodepleting chemotherapy, or pre-CTL019

[redacted]

infusion visit if no lymphodepleting chemotherapy was given) and through the Month 12 visit must be reported to Novartis within 24 hours of learning of its occurrence.

8.2.2.1 Screening/pre-treatment

Any SAEs experienced during the screening/pre-treatment phase (from the time of patient providing informed consent/assent until the patient begins study-related treatment) should ONLY be reported to Novartis and be captured in the CRF and safety database if the event meets at least one of the following criteria:

- All events leading to death.
- All pulmonary or cardiac abnormalities
- All infections
- All events related to a study procedure
- Any AE reportable for this study period that also meets criteria for serious
- Any substantial change in the status of the patient that precludes the patient from proceeding to study treatment (e.g. GVHD, rapid progression of malignancy, marked decline in performance status)
- Any other substantial change in the status of the patient that the investigator deems may have a potential impact on the patients during lymphodepletion and CTL019 treatment

8.2.2.2 Study-related treatment to Month 12

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has begun study-related treatment (i.e. lymphodepleting chemotherapy, or pre-CTL019 infusion visit if no lymphodepleting chemotherapy was given) and through the Month 12 visit must be reported to Novartis within 24 hours of learning of its occurrence.

8.2.2.3 Month 12 to Month 60

Any SAEs experienced after the Month 12 visit, and through the Month 60 (EOT) visit should only be reported to Novartis and recorded in the Adverse Events CRF if it meets one of the following criteria:

- Events leading to death
- Events related to a study procedure
- Infections:
- Serious or opportunistic infections that fulfill one of the following criteria:
  - Require anti-infective treatment OR
  - Lead to significant disability or hospitalization OR
  - Need surgical or other intervention
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of other hematologic disorder
- Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy

[redacted]

- Positive RCL test result
- Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene
- New malignancy (T-cell & non T-cell), other than the primary malignancy
- Progressive multifocal leucoencephalopathy (PML)
- Hepatitis B reactivation

In addition, at the specific request of a National Health Authority, the following SAEs will be reported in an expedited manner:

- Any SAE related to a study procedure
- All occurrences of CRS grade ≥ 3 (to be reported to National Health Authority on a monthly basis)
- All occurrences of Neurologic toxicity ≥ 4
- All deaths regardless of attribution following lymphodepleting chemotherapy and/or CTL019 infusion

8.2.2.4 Post-treatment protocol

Any SAEs experienced after the Month 60 (EOT) visit should only be reported to Novartis Drug Safety and Epidemiology (DS&E) if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE 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 should be reported separately as a new event.

In addition, semiannual and annual evaluations will be performed for up to 15 years from the date of infusion on all patients under a separate long term follow-up (LTFU) protocol as recommended by health authority guidance for patients treated with gene therapies. All patients who either complete or prematurely discontinue from the study will be enrolled in this destination protocol at the time of study completion/discontinuation (a separate informed consent form will be provided for this protocol; Section 7.1.7).

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

[redacted]

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis DS&E 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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable

8.4 Contraception

The contraceptive measures outlined in this section for WOCBP and sexually active males are the effective ones and they replace those presented in the Inclusion Criteria section.

WOCBP

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception for at least 12 months following CTL019 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 patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before enrollment into this study.

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

Sexually active males

Sexually active males must use a condom during intercourse for 12 months after the CTL019 infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests. qPCR

[redacted]

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.

8.5 Pregnancies

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

Pregnancy follow up in this study will end after birth or after any adverse pregnancy outcome associated with the end of the pregnancy. In case of live birth the newborn will be followed up until 12 months of age to detect any developmental issue or abnormality that would not be seen at birth. Pregnancy outcomes must also be collected for the female partners of any males who received CTL019 in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form 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 between the investigational treatment and pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.6 Warnings and precautions

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

8.7 Data Monitoring Committee

A data monitoring committee (DMC) will be established prior to the enrollment of the first patient. The DMC will be responsible for reviewing the safety and efficacy results from the interim analysis as well as overseeing safety data at regular intervals. Enrollment will not be interrupted in between the interim analysis data cutoff date and a DMC review of the interim analysis data and determination on whether to proceed with the study. The DMC will consist of members who are not involved in patient recruitment or trial conduct, with at least two oncologists (at least one adult hematologist/oncologist) and one biostatistician.

There will be an initial meeting with the DMC to have agreement on their roles and responsibilities and potential data format and procedures that will be reviewed during the course of the study. The first DMC safety review meeting will be held when approximately the first 5 patients have been treated for at least 1 month or at least 6 months after the first patient is enrolled, whichever occurs first. Subsequent safety reviews will occur every six months, unless otherwise requested by the Chairman of the DMC. Additional meetings will be held by DMC

[redacted]

or sponsor's requests at the time of some safety issues occurrence, especially when serious events (e.g., death) occur on the study or safety notifications regarding the study treatment come out.

Detailed recruitment status and interim safety reports will be provided to the DMC on a regular basis.

Further details regarding the constitution of the DMC and its specific roles will be provided in the DMC charter prior to the enrollment of the first patient.

8.8 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, Novartis representatives from the Clinical Trial team and not members of the DMC. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

8.9 Independent Review Committee (IRC)

An IRC will be established to review data related to disease response assessments during the Treatment and Primary Follow-up Phase and determine response and relapse for the primary analysis. An IRC charter will detail the IRC data flow and review process in alignment with the response definitions in Section 14.1. Patient management will be based upon local investigator assessments. The designation of response and relapse for the primary analysis and other related secondary efficacy endpoints will be based only on the evaluations made by the IRC. Details regarding the constitution of the IRC and its specific roles will be documented in the IRC charter agreed upon between Novartis and the IRC before initiation of any IRC reviews.

8.10 Follow-up of Secondary Malignancy

For patients treated with CTL019, treating physician/healthcare providers should contact Novartis if the patient develops a secondary malignancy.

Upon clinical confirmation of a secondary malignancy, blood samples should be collected for CAR-transgene and RCL.

Novartis strongly recommends collection of a portion of a biopsy (e.g., bone marrow, solid tumor) from the secondary malignancy (if applicable and previously collected as standard of care in diagnosing or treating the secondary malignancy) for analysis, such as CAR-transgene and RCL. Additional details for sample handling and shipping are outlined in the laboratory manual.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol 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.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

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

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

9.4 Database management and quality control

For studies using eCRFs, 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.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Data from all participating centers will be combined.

The primary analysis will be performed when 80 patients have received CTL019 infusion in the main cohort and completed 3 months from study day 1 infusion or discontinued earlier. Selected efficacy and safety analysis will be updated annually. A final Clinical Study Report (CSR) will be produced once all patients complete the study.

10.1 Analysis sets

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

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

[redacted]

10.1.1 Screened Set

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

10.1.2 Enrolled Set

The enrolled set comprises all patients who are enrolled in this study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients' apheresis product is accepted for manufacturing.

10.1.3 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received an infusion of CTL019

10.1.4 Safety Set

The Safety Set comprises all patients who received infusion of CTL019.

10.1.5 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).

Major protocol deviations leading to exclusion from the PPS include:

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

In addition, patients who receive a dose less than the minimum dose of 1×10^8 CTL019 transduced viable T cells will also be excluded. The detailed exclusion criteria of PPS will be determined and documented in the study Report and Analysis Plan (RAP) prior to primary analysis.

10.1.6 Pharmacokinetic analysis set

The CTL019 pharmacokinetic analysis set (PAS) consists of patients in FAS who have at least one sample providing evaluable pharmacokinetic (PK) data. The PAS will be used for summaries (tables and figures) of PK data.

[redacted]

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

[redacted]

10.2 Patient demographics/other baseline characteristics

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

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

Patients will be classified by their prior treatment response:

- Primary refractory: Patients who have never achieved CR prior to study
- Relapse without HSCT: Patients without SCT, had a CR from other therapy and relapsed prior to the study
- Relapse disease after prior autologous SCT

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

Prior and concomitant medications and significant non-drug therapies prior to and after the start of infusion will be listed by patient and summarized by the Anatomical Therapeutic Chemical (ATC) term. Transfusion during the study will be listed. [redacted]

10.4 Primary objective

The primary objective of the study is to evaluate the efficacy of CTL019 therapy as measured by overall response rate (ORR) rate, which includes complete response (CR) and partial response (PR) as determined by IRC assessment in the FAS for the main cohort.

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

10.4.1 Variable

The primary endpoint is the ORR as determined by IRC assessment. The ORR is defined as the proportion of patients with a best overall disease response of CR or PR, where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until progressive disease or start of new anticancer therapy, whichever comes first.

The overall response at each assessment is determined as in Table 10-1. For time points when both FDG-PET and CT are available, the FDG-PET assessment overrules the CT response.

[redacted]

Table 10-1 Overall response assessment

		FDG-PET based response	CT-based response
CMR/CR		**Complete Metabolic Response (CMR) (All of the following)**	**Complete Radiologic Response (CR) (All of the following)**
	Index nodal/extranodal (including splenic and hepatic lesions)	Score 1 or 2 with or without a residual mass on 5-PS Residual masses allowed if no PET-avid	Nodal Disease: ≤ 1.5 cm in LDi Extranodal Disease: Absent
	Non-index (including splenic and hepatic lesions)		Absent
	Spleen		Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow. Normal by morphology; if indeterminate, IHC/FLOW negative.	Normal by morphology; if indeterminate, IHC/FLOW negative.
PMR/PR		**Partial Metabolic Response (PMR) (All of the following)**	**Partial Remission (PR) (All of the following)**
	Index nodal/extranodal (including splenic and hepatic lesions)	Score of 3, 4 or 5 with reduced uptake compared to baseline with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. It is expected that there will be residual mass(es) present.	≥ 50% decrease from baseline in SPD of all index lesions
	Non-index (including splenic and hepatic lesions)		No increase
	Spleen		> 50% decrease from baseline in enlarged portion of spleen (value > 13 cm)
	New lesions	None	None
	Bone marrow	● Residual uptake higher than uptake in normal marrow but reduced compared with baseline ● Persistent focal changes in the marrow with nodal response,	Not applicable
NMR/SD		**No Metabolic Response (NMR) (All of the following)**	**Stable Disease (SD) (All of the following)**
	Index nodal/extranodal (including splenic and hepatic lesions)	Score of 3, 4 or 5 with no significant change in FDG uptake from baseline	<50% decrease from baseline in SPD of all index lesions No criteria for PD are met
	Non-index (including splenic and hepatic lesions)		No progression

[redacted]

		FDG-PET based response	CT-based response
	Spleen		No progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
PMD/PD		**Progressive Metabolic Disease (PMD) (At least one of the following)**	**Progressive disease (PD) (At least one of the following)**
	Index nodal/extranodal (including splenic and hepatic lesions)	Score of 3, 4 or 5 with increased uptake compared to the visually determined nadir with respect to SUV intensity or extent. This may apply to the specific hot spot and/ or overall the subject. and/or ● New FDG-avid foci consistent with lymphoma ● Consider biopsy or interval scan if etiology of new lesions uncertain	PPD Progression: An individual node/lesion must be abnormal with: ● LDi > 1.5 cm AND ● Increase by >= 50% from PPD nadir AND ● An increase in LDi or SDi from nadir ● ≥ 0.5 cm for lesions ≤ 2.0 cm ● ≥ 1.0 cm for lesions > 2.0 cm
	Non-index (including splenic and hepatic lesions)		Unequivocal Progression
	Spleen		Progression of existing splenomegaly New or Recurrent splenomegaly
	New lesions		Regrowth of previously resolved lesions New node > 1.5 cm in any axis New extranodal site > 1.0 cm in any axis New extranodal site < 1.0 cm in longest axis and unequivocal/attributable to lymphoma. Any size assessable disease unequivocal/attributable to lymphoma
	Bone marrow	New/recurrent FDG-avid foci	New/recurrent involvement

†PET 5PS: 1, no uptake above background; 2, uptake mediastinum; 3, uptake > mediastinum but liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma. SPD: Sum of the Products of Diameters; LDI: Longest transverse Diameter of a lesion; PPD: Product of perpendicular diameters

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

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

A best overall disease response of **SD** will be declared when at least one SD assessment is available at least 4 weeks after CTL019 infusion (and the patient would not qualify for CR or PR).

A patient will have a best overall disease response of **PD** if the progressive disease was observed less than 14 weeks after CTL019 infusion (and the patient does not qualify for CR, PR or SD).

[redacted]

If a patient does not qualify for CR, PR, SD or PD, then their best disease response will be **Unknown** (UNK).

See Section 14.1 for details of disease response criteria.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that ORR is greater than 20% at overall one-sided 2.5% level of significance, i.e.,

$$H_0: p \leq 0.2 \text{ vs. } H_a: p>0.2$$

The ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. The study will be considered successful if the lower bound of the 2-sided 95% exact confidence interval for ORR is greater than 20%, so that the null hypothesis that the ORR is less or equal to 20% can be rejected.

The primary efficacy endpoint, ORR will be analyzed based on the data observed in the FAS.

10.4.3 Handling of missing values/censoring/discontinuations

Patients in this study who are of unknown clinical response will be treated as non-responders. See also the Novartis guideline for efficacy evaluation in DLBCL and FL studies [redacted] (Appendix 1) for more details.

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

10.4.4 Supportive analyses

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

10.4.4.1 Subgroup analysis

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

- Age: < 40 years, ≥40 years to <65 years, ≥ 65 years
- Gender: Male, Female
- Race: Asian, Black, Caucasian, Native American, Other, Pacific Islander, Unknown
- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- Prior response status: Primary refractory, relapse without SCT, relapse after SCT
- IPI at enrollment: <2 risk factors, ≥2 risk factors
- Number of prior lines of anti-neoplastic therapy: ≤2 lines, 3 to4 lines, >4 lines
- Stage of disease at baseline: I/II, III/IV.

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

[redacted]

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

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

10.5.2 Other secondary efficacy objectives

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

10.5.2.1 Duration of overall response (DOR)

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

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling HSCT)
- Event documented after at least two missing tumor assessments
- Adequate assessments no longer available

In the main analysis of DOR, death due to reason other than DLBCL will be considered as a competing risk event to other events of interest (progression or death due to DLBCL). In this analysis, the median response duration as well as proportion of patients without events following response (progression or death due to DLBCL) at 3, 6, 9, 12 months, etc. will be presented with 95% confidence intervals using the cumulative incidence function (CIF). Distribution of DOR will also be estimated using the Kaplan-Meier method in which death due to reason other than DLBCL will be censored.

As HSCT is an important treatment option in responding patients, it is appropriate to consider the date of HSCT as censoring date, instead of censoring at the last tumor assessment date. If a patient received HSCT after a CR or PR, relapse or survival status after HSCT will be recorded on the corresponding follow-up eCRFs, although data on individual disease response components (e.g. CT scan) will not be collected. In such cases, the date of relapse or death (if due to DLBCL) after HSCT will be used for the calculation of DOR as a sensitivity analysis.

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

[redacted]

In addition, the DOR may be separately summarized for patients with best overall response of CR and those with best overall response of PR.

10.5.2.2 DOR will be analyzed by cohort as well as for all treated patients combined in FAS.Event free survival (EFS)

Event free survival (EFS) is the time from date of first CTL019 infusion to the earliest of the following:

- Death from any cause
- Disease progression or relapse
- New anticancer therapy for lymphoma, excluding HSCT

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- HSCT (see below for handling of HSCT)
- Event after at least two missing scheduled disease assessment
- Adequate assessments no longer available

In the main analysis of EFS, patients who proceed to HSCT after CTL019 infusion will be censored at the time of HSCT. In addition, a sensitivity analysis of EFS will be performed without censoring for HSCT.

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

EFS will be analyzed by cohort as well as for all treated patients combined in FAS.

10.5.2.3 Progression free survival (PFS)

Progression-free survival (PFS) is defined as the time from the date of first CTL019 infusion to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of the last adequate assessment.

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (see below for handling of HSCT)
- Event documented after at least two missing tumor assessments
- Adequate assessments no longer available

[redacted]

In the main analysis of PFS, patients who proceed to HSCT after CTL019 infusion will be censored at the time of HSCT. In addition, a sensitivity analysis of PFS will be performed without censoring for HSCT.

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

PFS will be analyzed by cohort as well as for all treated patients combined in FAS.

10.5.2.4 Time to response

Time to overall disease response (CR or PR) is defined as the time from the date of CTL019 infusion to the date of first documented disease response (CR or PR). The analysis will include all responders.

Time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with a 95% confidence interval.

10.5.2.5 Time to response will be analyzed by cohort as well as for all treated patients combined in FAS.Overall survival (OS)

Overall survival (OS) is the time from date of first CTL019 infusion to date of death due to any reason. If a death has not been observed by the date of analysis cutoff, OS will be censored at the date of last contact.

OS will be assessed in all patients (FAS). The distribution function of OS will be estimated using the Kaplan Meier (KM) method. The median OS and the proportion of patients alive at 3, 6, 12, 18, 24, 36, 48 and 60 months with 95% confidence intervals will be presented.

OS will be analyzed by cohort as well as for all treated patients combined in FAS.

10.5.2.6 Efficacy in histological and molecular subgroups

ORR, PFS, OS, EFS, and DOR will be descriptively summarized in histological subtypes (NOS, other) and molecular subtypes (GC, ABC and other).

10.5.2.7 Overall response rate in all treated patients

Overall response rate in all treated patients in FAS will be summarized along with the 95% confidence interval.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used, unless otherwise specified. All listings and tables will be presented by one treatment arm of CTL019.

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

[redacted]

- Pre-treatment period: from day of patient's informed consent to the day before first lymphodepleting chemotherapy dose or the pre-infusion visit if the lymphodepleting chemotherapy is not given.
- Lymphodepleting period (note: this period only applies to patients who received lymphodepleting chemotherapy): from the first day of lymphodepleting chemotherapy
  - to the day before infusion of CTL019, for patients who received infusion, or
  - to the earlier of date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy for patients who didn't receive infusion of CTL019
- Post-infusion period: starting at day of CTL019 infusion

10.5.3.2 Adverse events (AEs)

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

Adverse events that begin or worsen after informed consent should be recorded in the patient's source documents. New or worsening adverse events prior to starting study treatment (i.e. lymphodepleting chemotherapy or the pre-infusion visit if the lymphodepleting chemotherapy is not given per Section 6.1.1.1) are not required to be recorded in the CRF unless it is an SAE meeting criteria outlined in Section 8.1.2 or SAE meeting criteria outlined in Section 8.2.2. Once the patient begins lymphodepleting chemotherapy or the pre-infusion visit, all new or worsening adverse events will be recorded in the Adverse Event CRF. Summary tables for adverse events will be provided for AEs that started or worsened during the post-infusion period, i.e. the CTL019-treatment-emergent AEs. In addition, AEs that started or worsened during the lymphodepleting period will be summarized for all patients who received lymphodepleting chemotherapy. All safety data (including those from the pre-treatment period) will be listed along with the period (as defined in Section 10.5.3.1) of the starting date of AE.

The incidence of CTL019 treatment-emergent adverse events (new or worsening during the post-infusion period) will be summarized by primary system organ class, preferred term, severity (based on CTCAE grades), and relation to study treatment. A patient with multiple 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 and serious adverse events will be listed by patient and tabulated by primary system organ class and preferred term.

Adverse events of special interest (AESI)

The current search criteria of AESI are based on limited experience from ongoing clinical studies without an accurate assessment of causality. AESI and the search criteria of AESI will be updated prior to reporting. AESI that occur within 8 weeks of the CTL019 infusion will be summarized by group term and preferred term.

[redacted]

10.5.3.3 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 be generated separately for hematology and biochemistry and laboratory tests:

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

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

[redacted]

10.5.3.4 Immunogenicity

Humoral immunogenicity assessment will include evaluation of pre-existing (pre-treatment) and post-treatment anti-CTL019 antibodies and to examine the incidence of immunogenicity with treatment, together with antibody titers, as a secondary endpoint. Data may be further fractionated to determine proportion of patients who make transient versus sustained antibody responses. The assay for humoral immunogenicity will be a cell-based assay, detecting antibodies that bind to a Jurkat cell line transfected with the CTL019 construct. This cell line stably expresses the complete CTL019 sequence and can be used to detect antibodies that bind to any epitope on the extracellular domain of the protein. [redacted]

10.5.3.5 Other safety data

Vital signs will be collected as clinically needed. Presence of detectable RCL will be tested by VSV-G at scheduled assessments in Table 7-1 and Table 7-2. All safety data will be listed.

10.5.3.6 Safety subgroup analysis

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

- Age: < 40 years, ≥ 40 years to <65 years, ≥ 65 years
- Gender: Male, Female
- Race: Asian, Black, Caucasian, Native American, Other, Pacific Islander, Unknown

[redacted]

- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- Prior HSCT therapy yes or no
- Histological (NOS, other) and molecular subgroups (GC, ABC, other)

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

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

Summary for AE will be separately performed for each cohort and for all patients combined in safety set.

10.5.4 Pharmacokinetics

CTL019 concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed and summarized by time points as assessed by the following:

- CTL019 transgene levels as measured by q-PCR
- CTL019 transduced cells measured by flow cytometry of CD3-positive

[redacted]

The PK parameters listed in Table 10-2 along with other relevant PK parameters will be estimated, if feasible, from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix® (Pharsight, Mountain View, CA) and reported by best response category. The non0-quantifiable concentrations will be imputed to zero for PK concentration summaries wand will not be included for estimation of PK parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and PK parameter derivations.

Table 10-2 Noncompartmental pharmacokinetic parameters

Parameter	Definition
AUC 0 - Tmax	The AUC from time zero to T_{max} in peripheral blood (%*days or days*copies/ µg)
AUC Tmax - 28d and/or AUCTmax-84d	The AUC from time Tmax to day 28 and/or AUCTmax-84dor other disease assessment days, in peripheral blood (%*days or days*copies/ µg)
AUC 0 - 28d and/or AUC0-84dand M3	The AUC from time zero to day 28 and/or day 84 and or other disease assessment days, in peripheral blood (%*days or days*copies/ µg)
Cmax	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (% or copies/ µg)
Tmax	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
T1/2	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
Clast	The last observed quantifiable concentration in peripheral blood (% or copies/µg)
Tlast	The time of last observed quantifiable concentration in peripheral blood (days)

[redacted]

Descriptive statistics of PK parameters will be summarized by arithmetic and geometric means, standard deviation, CV%, CV% geometric mean minimum, median and maximum. For Tmax only minimum, median and maximum will be presented. PK parameters will also be summarized by best overall response.

[redacted]

If there is sufficient data available additional summaries and/or model-based analyses relating exposure to clinical response, CRS grade or other endpoints of interest may be considered. Further details will be provided in the RAP. [redacted] Population PK and/or PKPD methods including covariate analysis may be utilized if supported by the data, and may be summarized in a report separate from the CSR.

[redacted]

Descriptive statistics of key PK parameters will be separately summarized for each cohort as well as for all treated patients in the Pharmacokinetic Analysis Set.

[redacted]

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

One interim analysis for futility and overwhelming efficacy is planned for the study when approximately 50 patients of the planned 80 (62.5%) in the main cohort have received CTL019 infusion and the last patient has completed 3 months from study day 1 infusion or discontinued earlier. An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in EAST 6.3, will be used to construct the efficacy stopping boundary (Lan and DeMets 1983). Based on this choice of α-spending function, if the interim analysis is performed with 50 patients, the lower bound of the 2-sided 99.08% exact confidence interval for ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 19/50=38% will be needed to claim success at interim analysis. At the final analysis when 80 patients are treated and followed for at least 3 months, 2-sided 95.28% exact CI will be used correspondingly, requiring an ORR of 24/80=30% to claim success.

The futility stopping boundary will be determined based on the predicted probability of success at the final analysis. The study may be stopped for futility if the posterior predictive probability of claiming success at the end of the study, i.e. observing at least 24 responders out of 80 total patients, is found to be smaller than 10% based on the data from interim analysis. Based on a non-informative prior (Beta (1,1)) on the probability of success, if less than or equal to 12 responders are observed from 50 patients in the interim analysis, then the Bayesian predictive probability of observing at least 24 responders from 80 patients at the end of the study will be less than 10%.

[redacted]

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

The above decision rules will be used by the DMC, to make recommendations to continue or stop the trial. The DMC will also review safety data periodically.

The operating characteristics of certain scenarios are summarized in Table 10-3 below.

Table 10-3 Simulated scenarios for interim and final analysis

Scenario	Simulated probability (%) to claim success at interim analysis	Simulated probability (%) to stop for futility at interim analysis	Simulated probability (%) to claim success at interim or final analysis
p=0.20 (H_0)	0.3	81.04	2.1
p=0.30	13.86	22.36	52.18
p=0.38	54.49	2.66	93.64
p=0.50	96.60	0.05	99.95

10,000 simulations were performed for each scenario using R 3.0.2.

10.8 Sample size calculation

In two retrospective studies in relapsed and refractory DLBCL patients receiving 2nd or 3rd line therapies, the observed ORR were 14% and 20% (Seshadri et al 2008, Elstrom et al 2010). In a recent prospective clinical trial with ibrutinib in patients who had a median of 3 prior lines of therapy, the ORR in the ABC subtype was 40% and in the GC subtype 5% leading to an overall ORR of 21.7% (Wilson et al 2012).

Based on the null hypothesis of ORR $\leq$ 20% and alternative hypothesis of ORR >20%, 80 patients in the primary analysis will provide 94% cumulative power to demonstrate statistical significance, using a 2-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary and an exact CI at one-sided cumulative 0.025 level of significance, if the underlying ORR is 38%. In this setting, an ORR of 24/80=30% will be needed to claim success.

Assuming approximately 20% enrolled patients will not be infused due to reasons such as manufactory failure, worsening of patient's condition, etc., at least 100 patients need to be enrolled in the main cohort to ensure 80 patients are treated and hence will be used for the primary analysis. At least 25 patients in each of the GC and ABC DLBCL subtypes will be treated in the main cohort.

10.9 Power for analysis of key secondary variables

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

[redacted]

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

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

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

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

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Male participants 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.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.3.

[redacted]

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

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

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

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

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

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

[redacted]

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis, with the exception of information required to ensure the chain of identity of the CTL019 product. This may include name, date of birth, medical record number and donor identification number. The level of detail disclosed will follow local regulations. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

[redacted]

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14 Appendices

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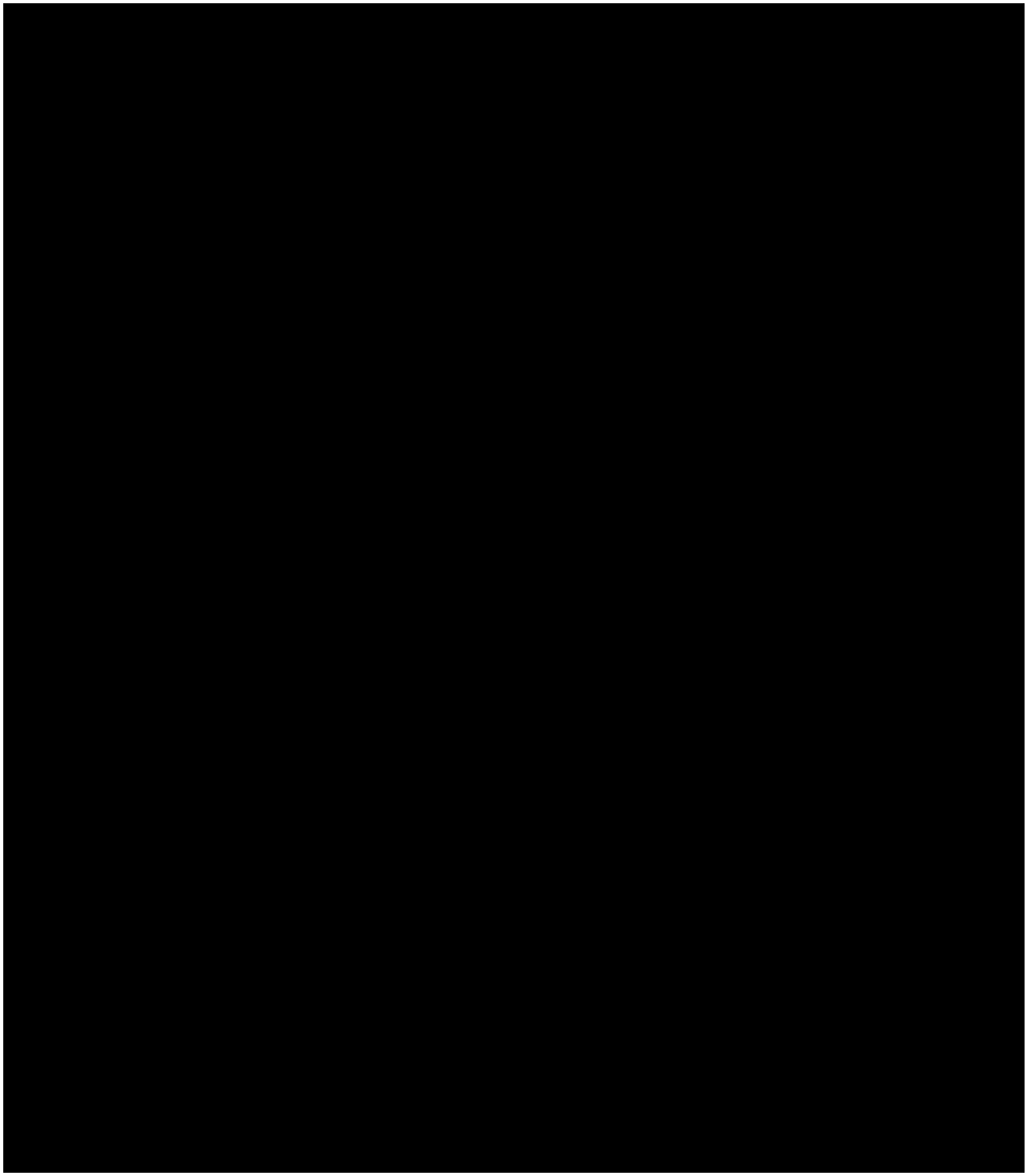

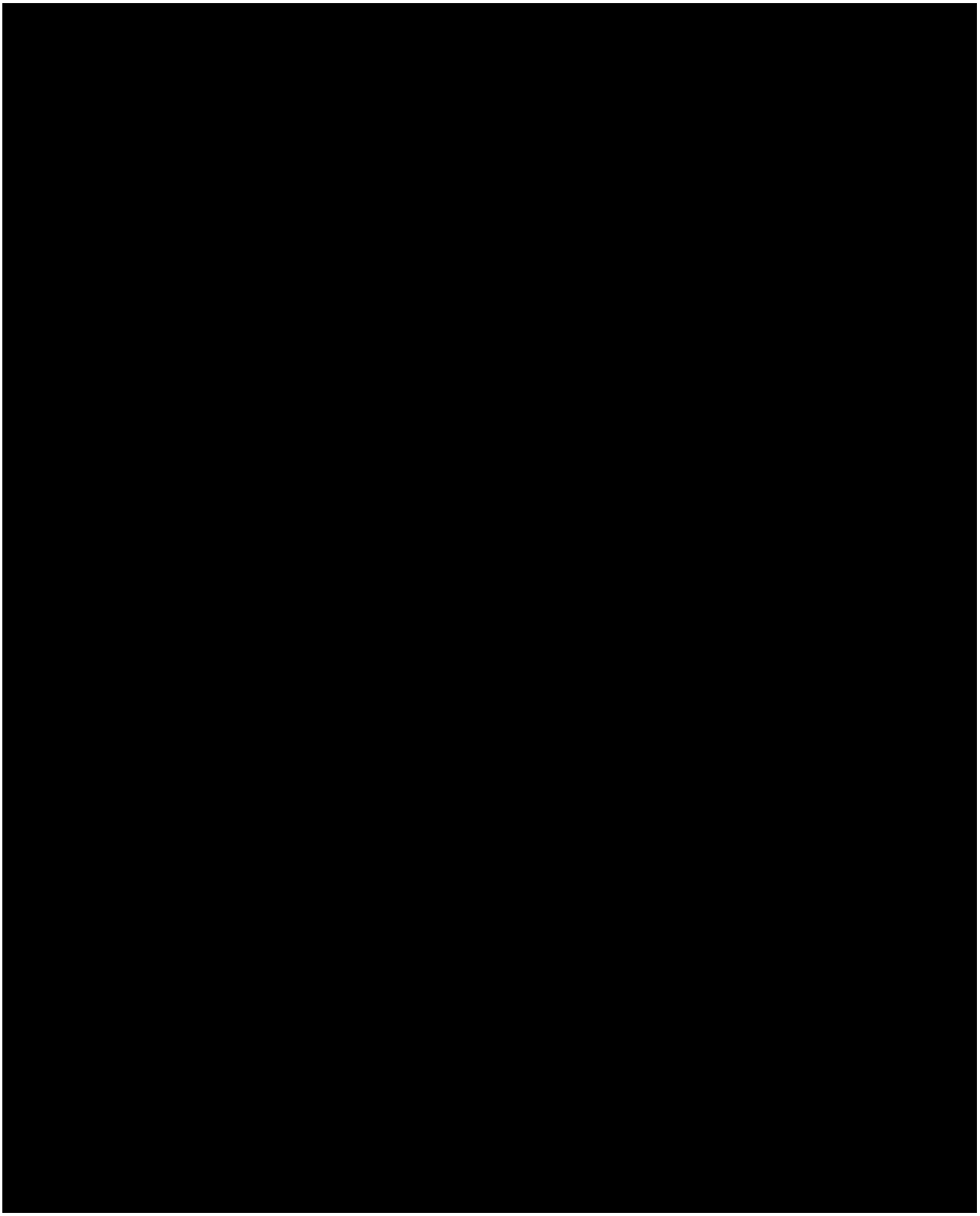

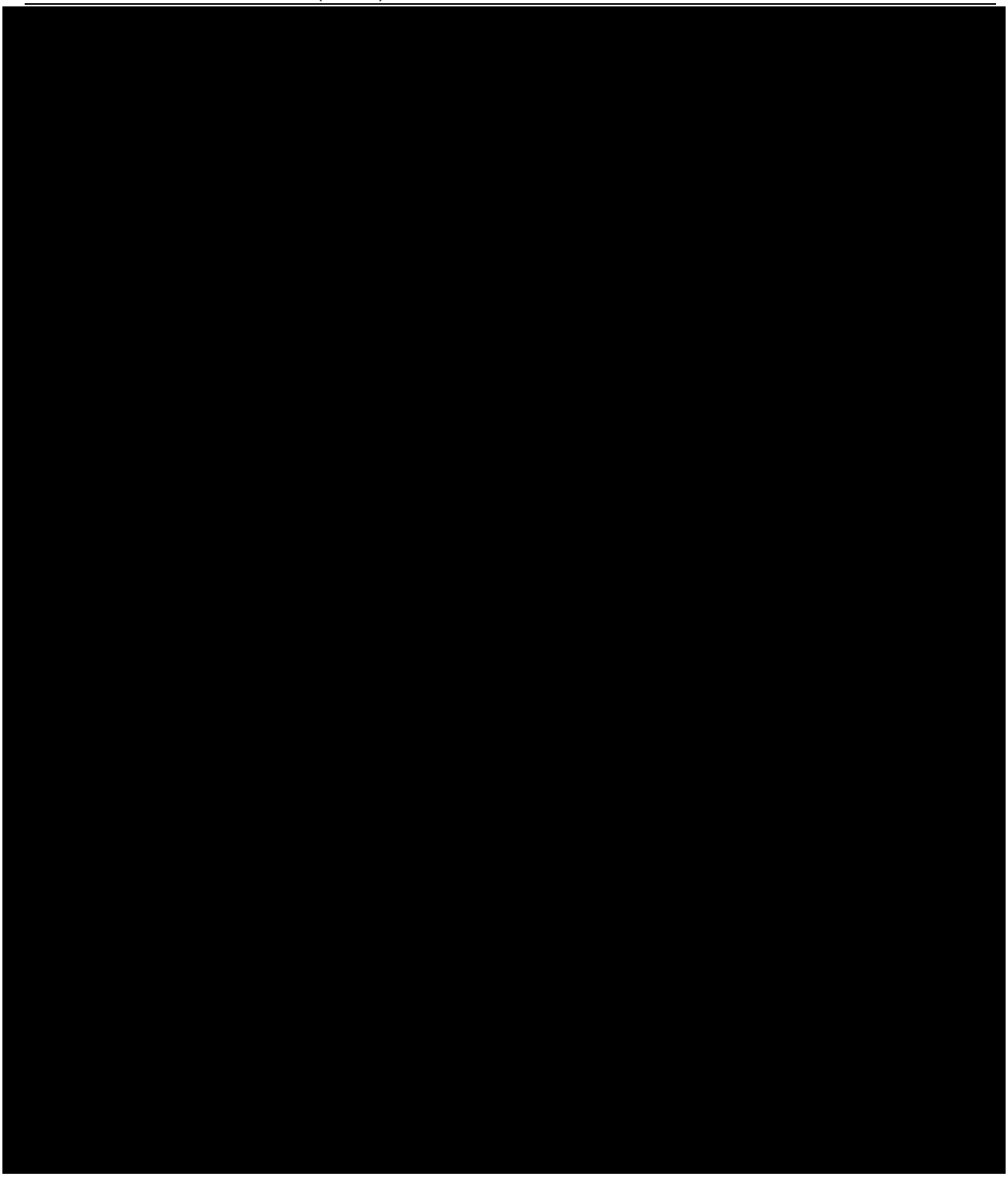

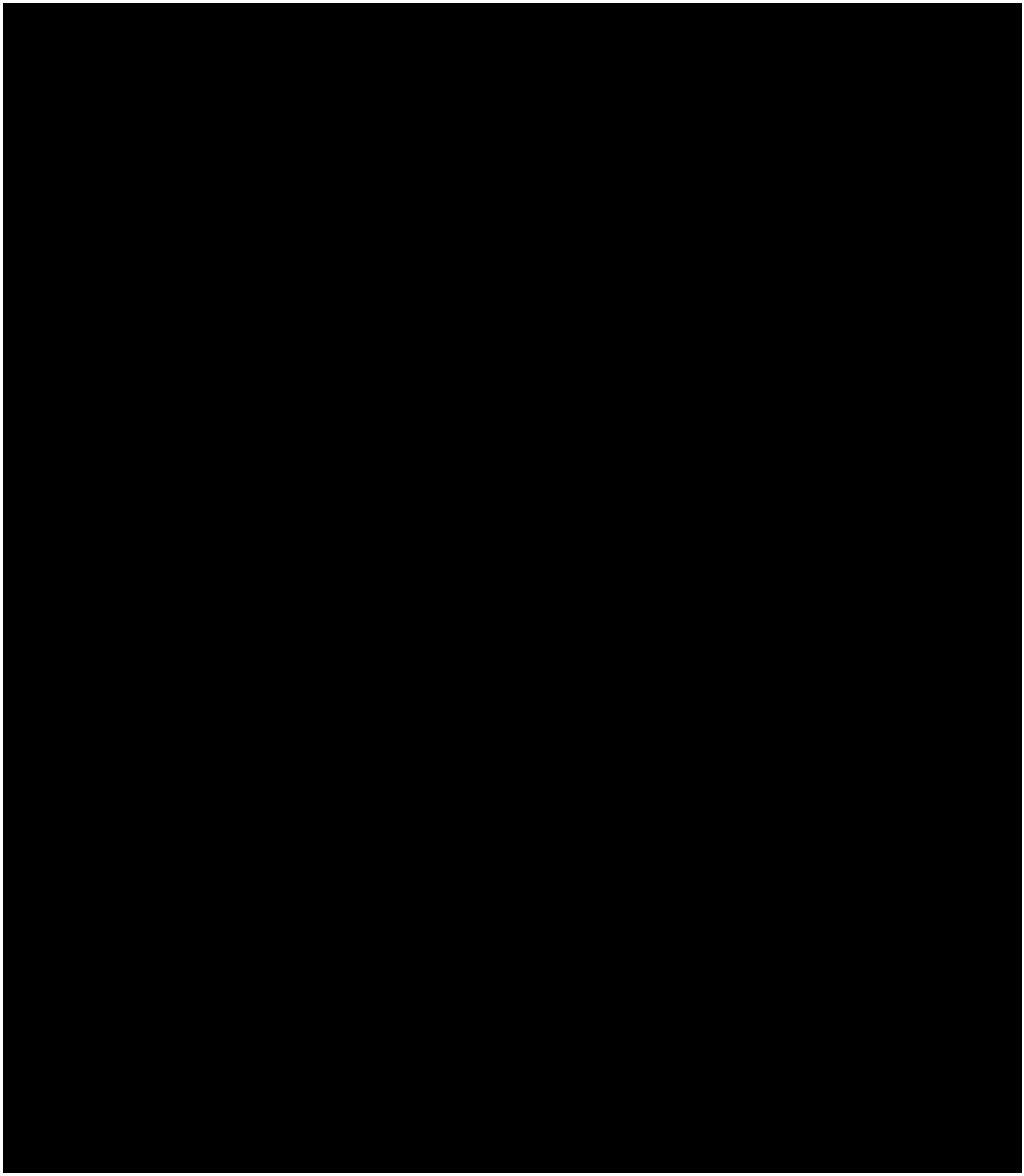

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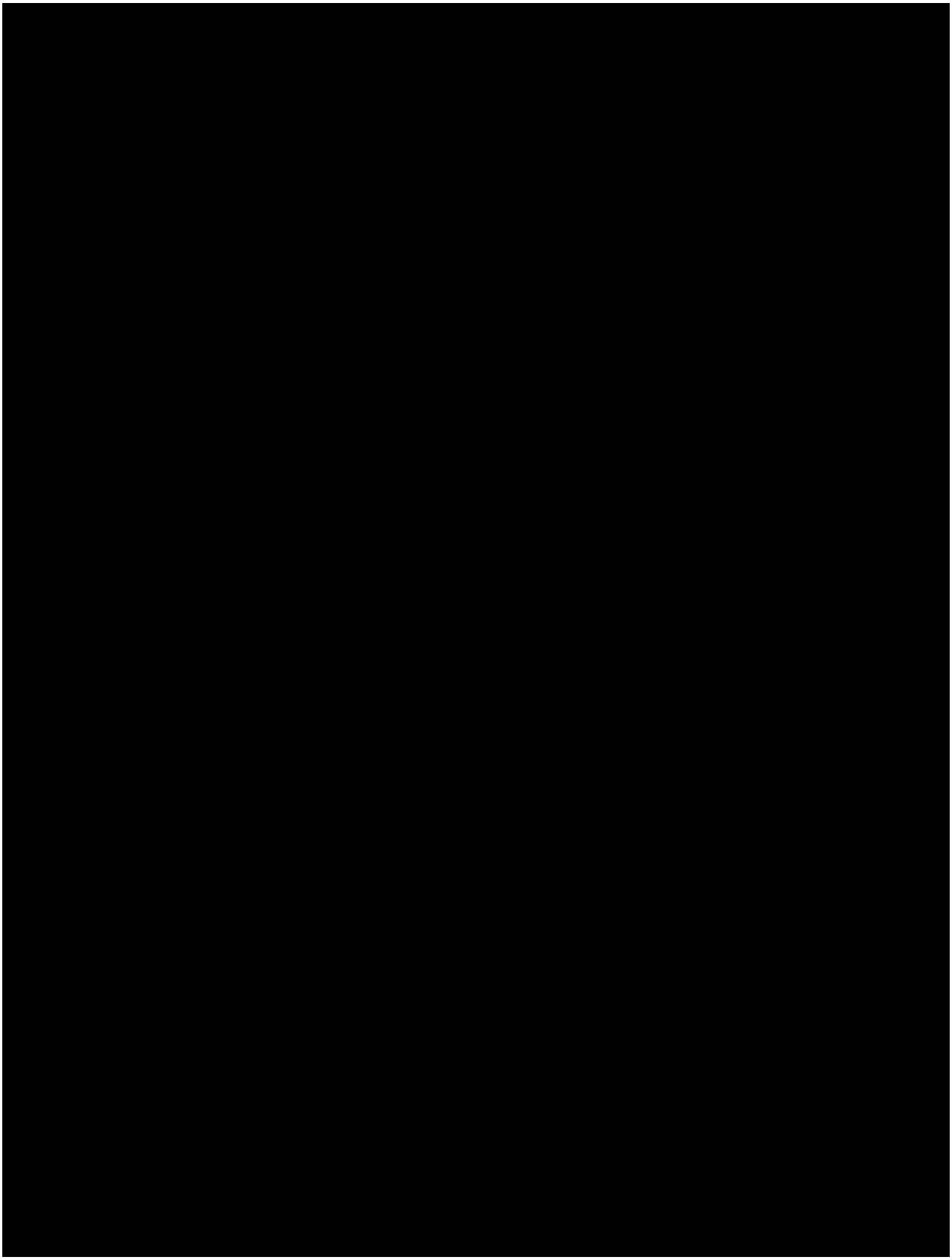

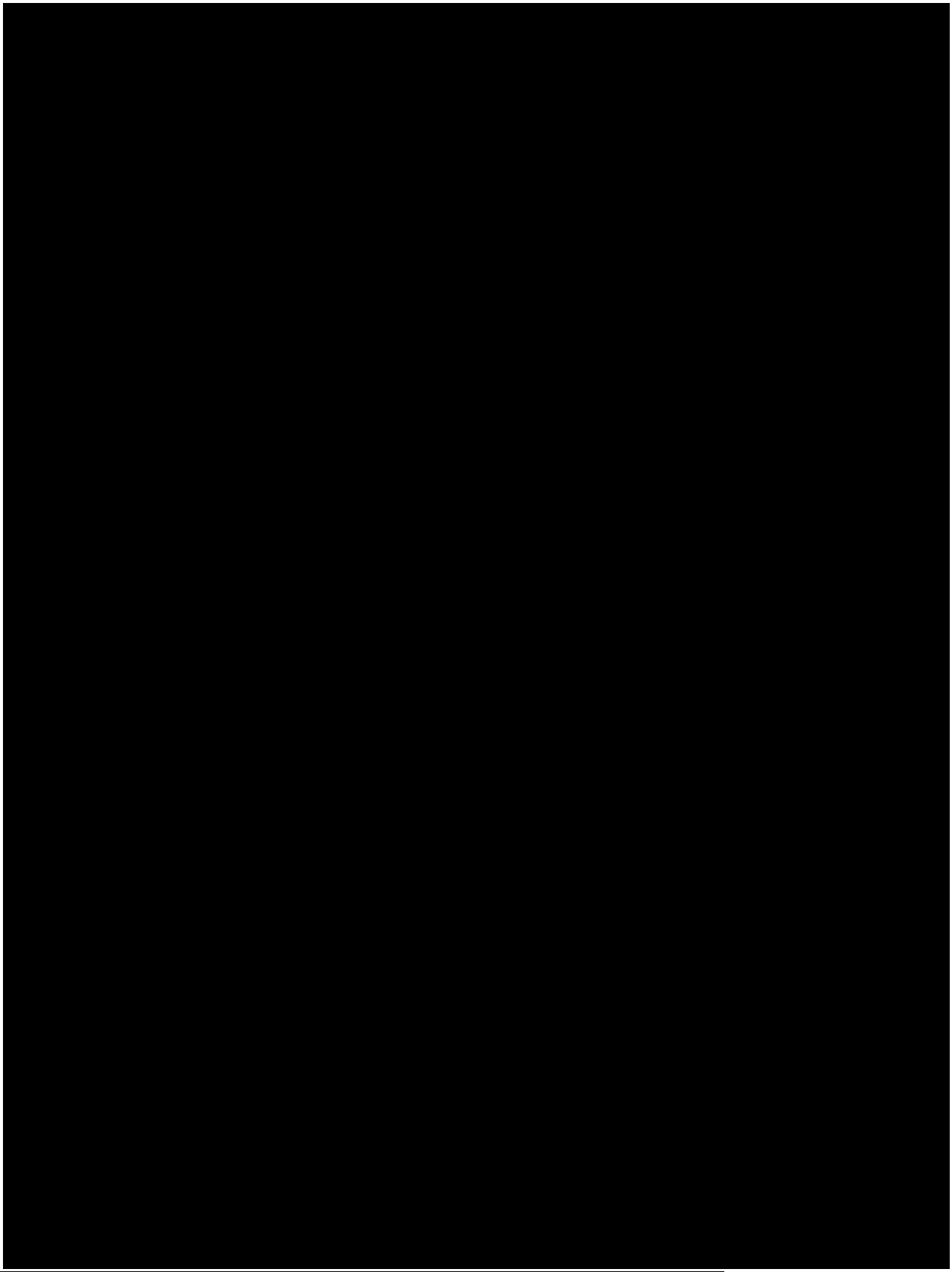

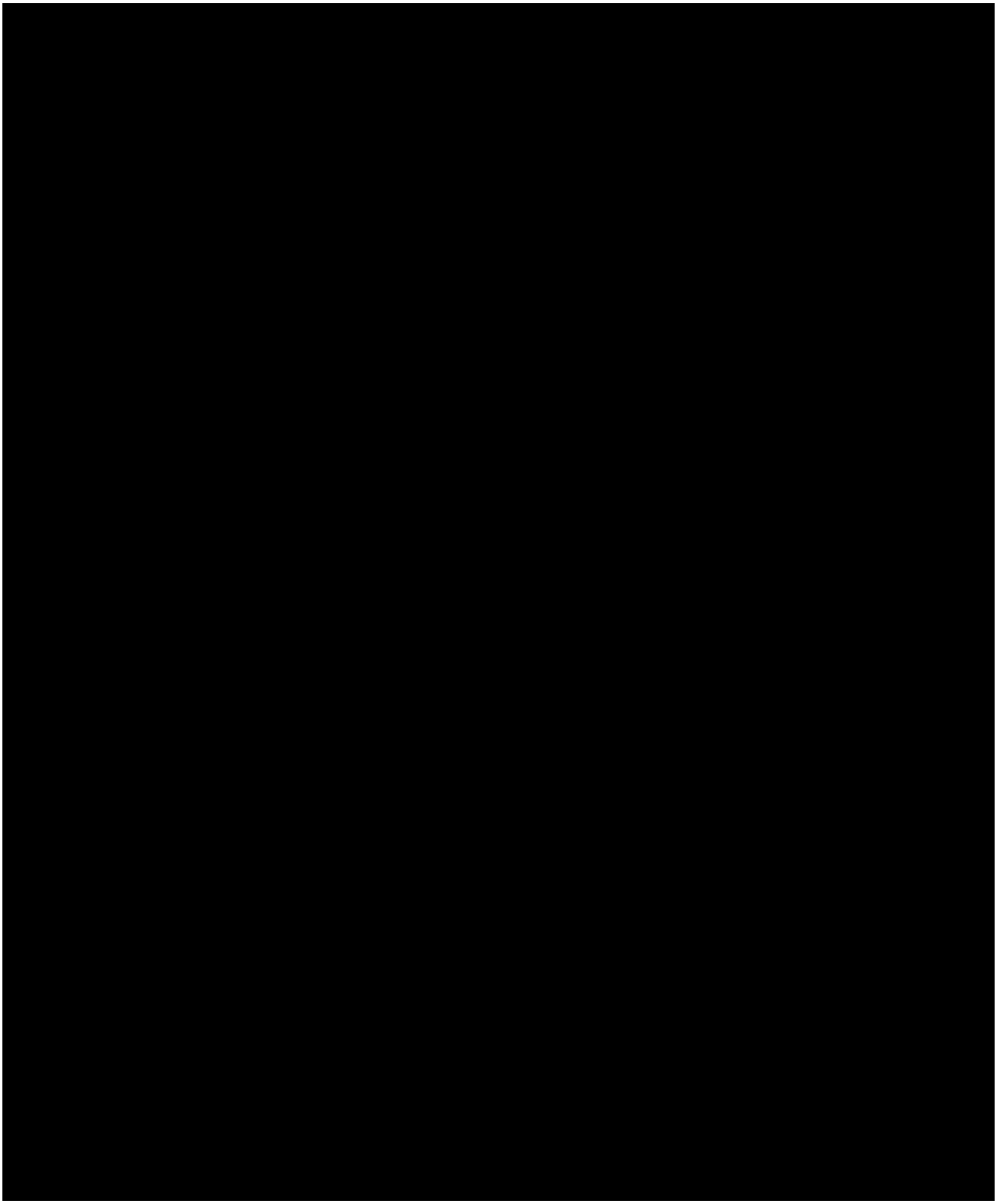

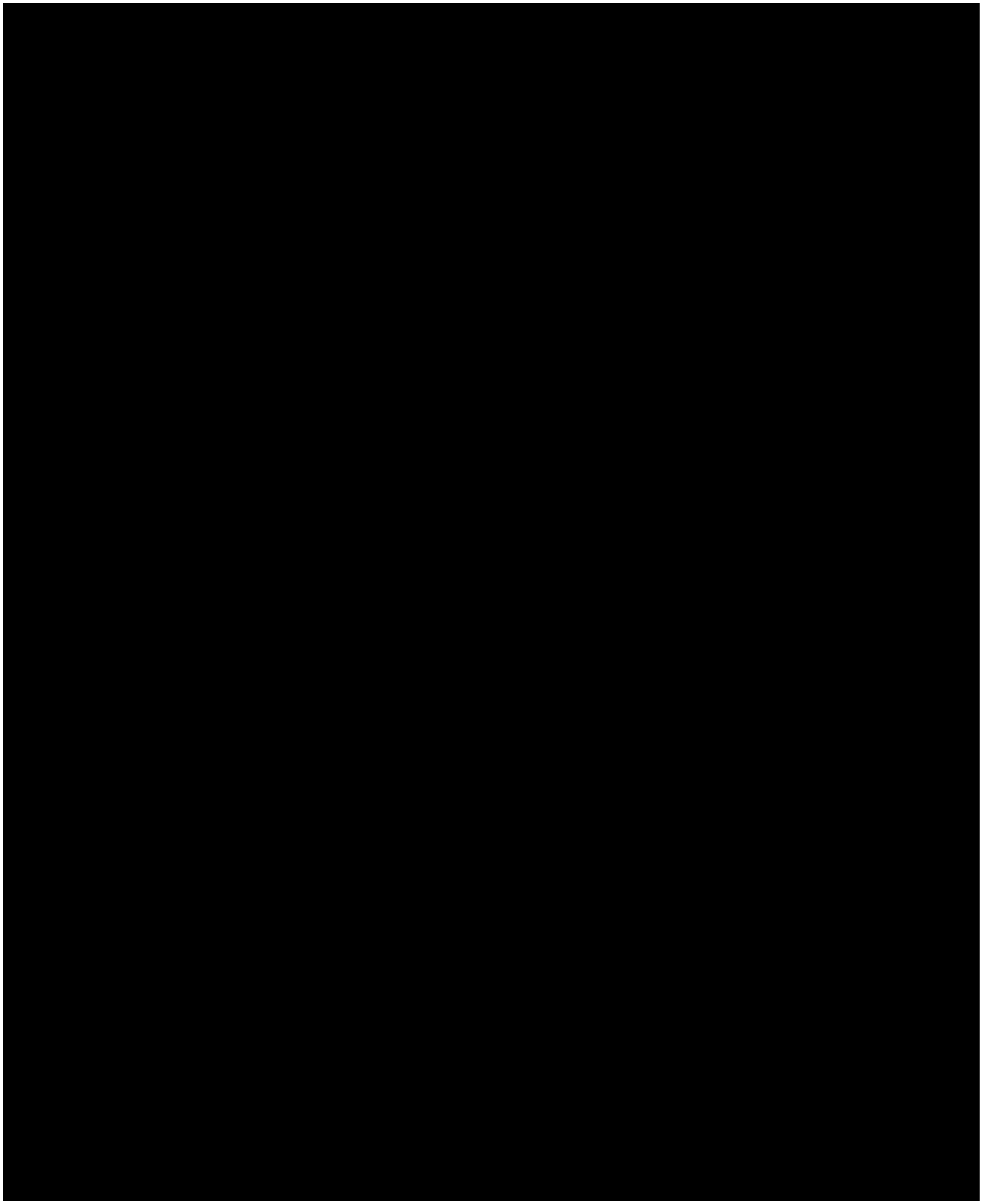

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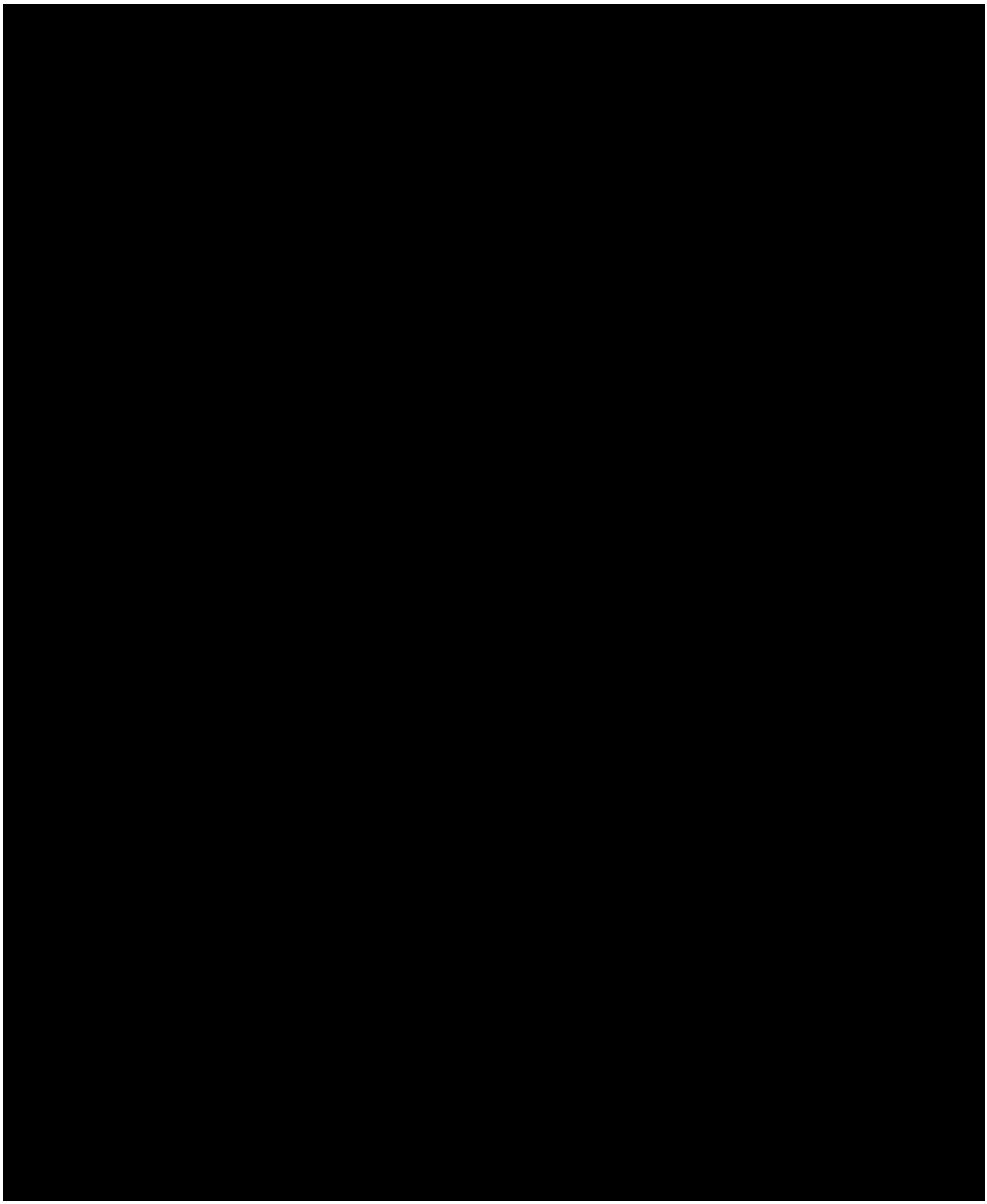

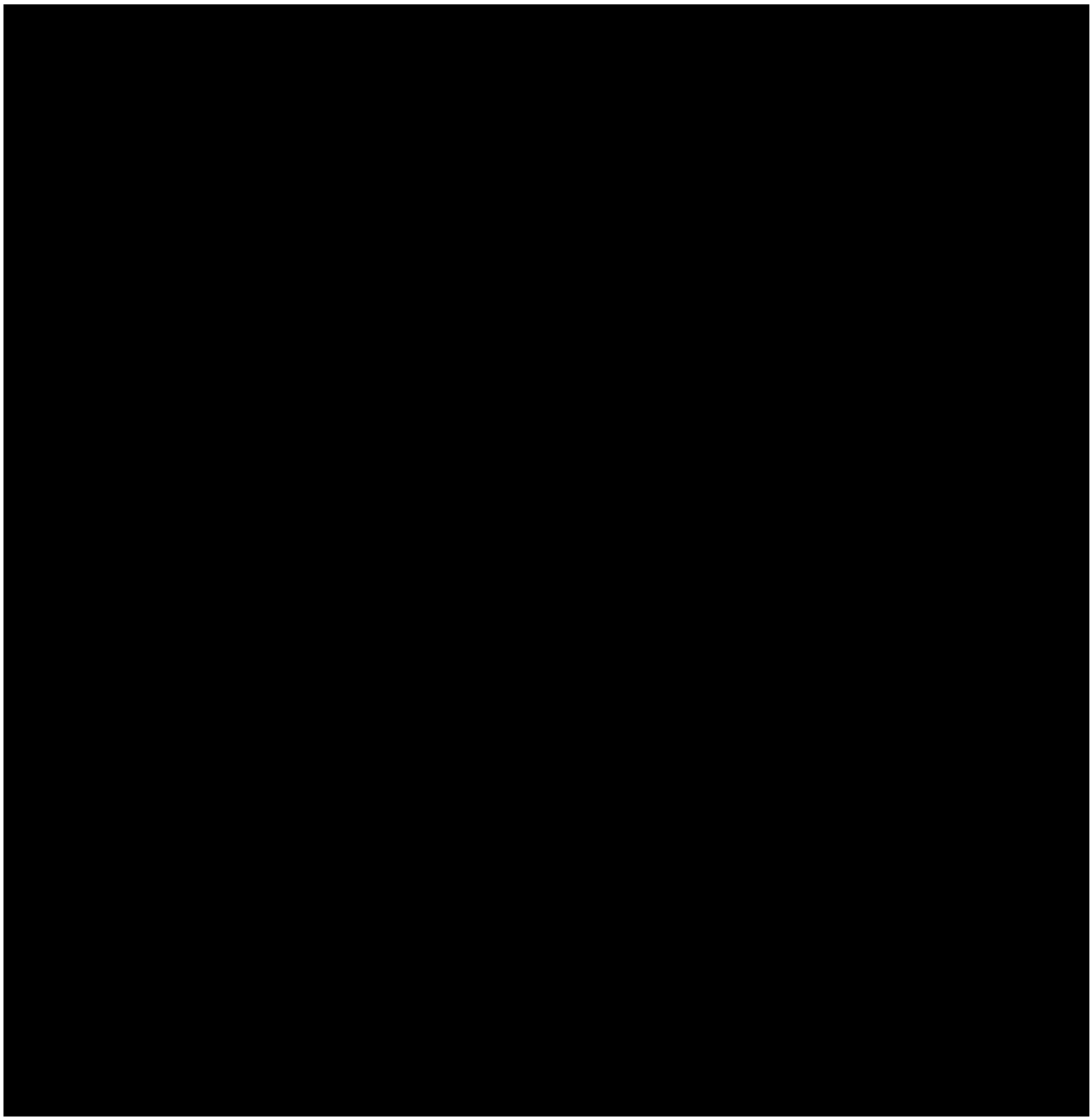

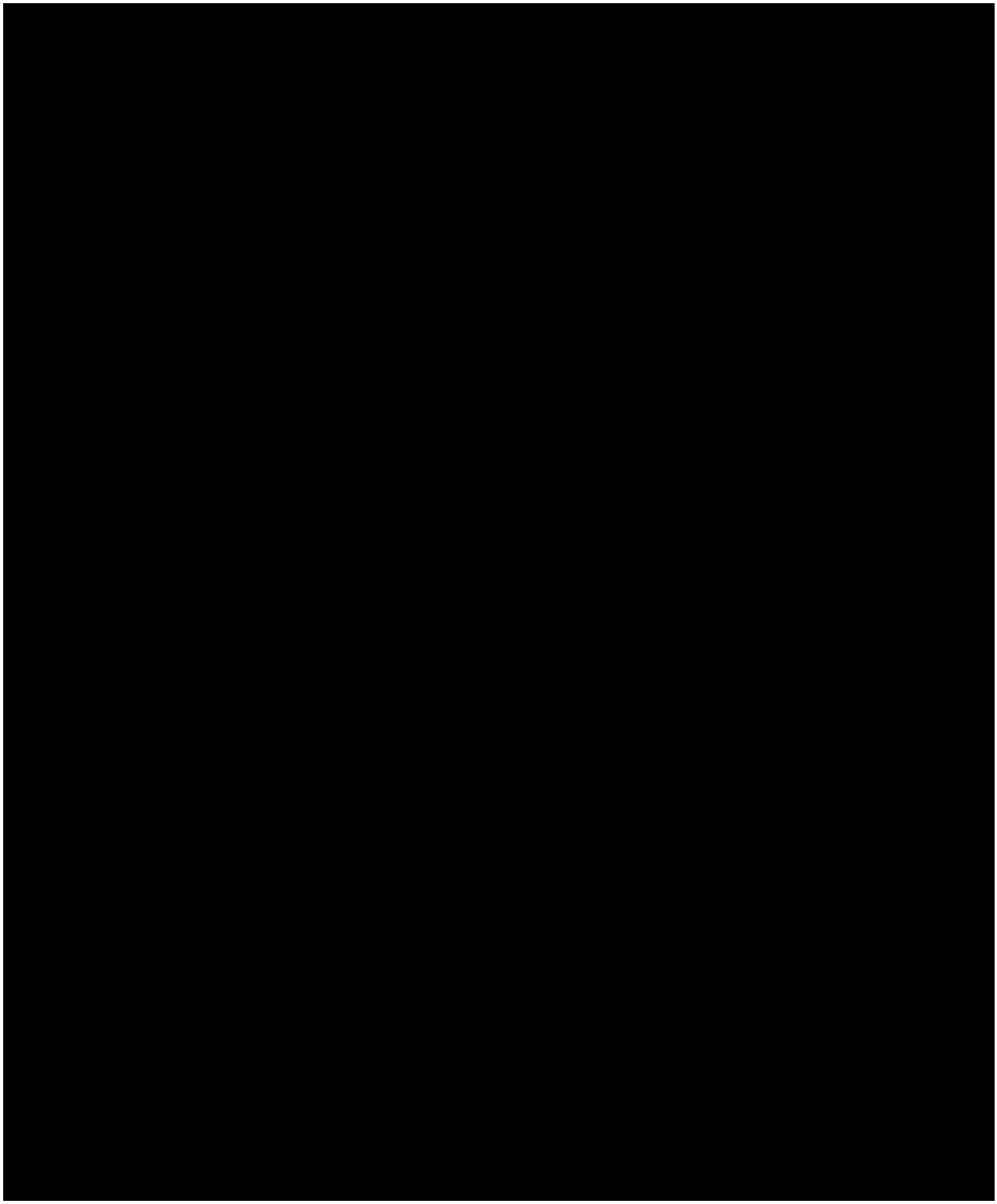

14.2 Appendix 2: Eligibility based on serologic markers for hepatitis B infection

Test	Results				
HBsAg	+	-	-	-	-
HBcAb	Any	+	+	-	-
HBsAb	Any	-	+	+	-
Eligibility	**Not Eligible**	**Not Eligible**	**Not Eligible**	**Eligible**	**Eligible**

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

Anti-HBs positive as the only positive marker: Protective – Indicates vaccination. These patients are eligible for this trial.

Anti-HBc positive (with or without HBsAb positive): Indicates prior infection and the possibility of recrudescent hepatitis B (including flare with acute liver failure). These patients are also at risk for viral reactivation. These patients are not eligible for this trial.

14.3 Appendix 3: CTL019 modified data reporting – Treatment and Primary Follow Up Phase

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

[redacted]

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

	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment Period** (Starting from LD chemo/pre-infusion visit)	**Post-treatment Period**
		Through Month 12 Visit	**After Month 12 Visit, through Month 60**
Non-serious Adverse Events (AE)	Modified: ● All infections ● All laboratory abnormalities deemed clinically significant by the investigator ● All clinical AEs grade ≥ 3 ● All AEs related to a study procedure ● All AEs leading to study discontinuation	All, including all laboratory abnormalities deemed clinically significant by the investigator	Modified –Whether serious or non-serious, report following: ● Events leading to death ● Related to a study procedure ● Infections ● Serious or opportunistic infections that fulfill one of the following criteria: Require anti-infective treatment OR Lead to significant disability or hospitalization OR Need surgical or other intervention ● New incidence or exacerbation of a pre-existing neurologic disorder ● New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder ● New incidence of other hematologic disorder ● Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy ● Positive RCL test result ● Vector insertion site sequencing result with a mono- or oligoclonality pattern or in a location near a known human oncogene ● New malignancy (T-cell & non T-cell), other than the primary malignancy ● Progressive multifocal leucoencephalopathy (PML) ● Hepatitis B reactivation
Serious Adverse Events (SAE)	Modified: ● All events leading to death ● All events related to a study procedure ● Any AE reportable for this study period that also meets criteria for serious ● All pulmonary or cardiac abnormalities ● All infections ● Any substantial change in the status of the patient that precludes the patient from proceeding to study treatment (e.g. GVHD, rapid progression of malignancy, marked decline in performance status) ● Any other substantial change in the status of the patient that the investigator deems may have a potential impact on the patients during lymphodepletion and CTL019 treatment	All	

[redacted]

14.3.2 Concomitant medication and laboratory reporting

	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment Period** (Starting from LD chemo/pre-infusion visit, through Month 12)		**Post-treatment Period** (After Month 12, through Month 60)
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**	**Inpatient/ICU OR Outpatient**
Concomitant medications	Modified: **Drugs:** Record **all** of the following medications: [redacted] ● 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).		All	Modified: ● Related to an AE or SAE defined as reportable for this period ● Mutagenic agents (including cytotoxic drugs) ● Radiation & antineoplastic therapy (including SCT) ● Immunoglobulin therapy ● Immunosuppressive agents (including dose of steroids higher than physiologic replacement therapy doses of steroids (< 12 mg/m2/day hydrocortisone or equivalent) ● Investigational therapy

[redacted]

	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment Period** (Starting from LD chemo/pre-infusion visit, through Month 12)		**Post-treatment Period** (After Month 12, through Month 60)
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**	**Inpatient/ICU OR Outpatient**
	● 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 **<u>Antibiotics:</u>** Record all antibiotics starting from day of infusion, even if given prophylactically			
Laboratory data	Modified: ● Record **all** scheduled labs (per Visit Evaluation Schedule) ● Record **all** results (scheduled or unscheduled) for: LDH, Uric acid, [redacted] and fibrinogen (related to CRS/TLS/MAS) ● Record all other laboratory values if they are ≥ Grade 3 ● For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled) ● For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia) ● Laboratory abnormalities that are not clinically significant and treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)		All	Modified: ● Record **all** scheduled labs (per Visit Evaluation Schedule) ● Record **all** results (scheduled or unscheduled) for: LDH, Uric acid, [redacted] and fibrinogen (related to CRS/TLS/MAS) ● Record all other laboratory values if they are ≥ Grade 3 ● For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled) ● For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia) ● Laboratory abnormalities that are treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)

[redacted]

14.4 Appendix 4: CTL019 modified data reporting – Secondary Follow Up Phase

Adverse Events/ Serious Adverse Events	Concomitant Medications
● New incidence or exacerbation of a pre-existing neurological disorder ● New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder ● New incidence of other hematologic disorders ● Any severe adverse event or condition the investigator believes may have a reasonable relationship to CTL019 therapy ● Any severe adverse event or condition that is unexpected ● Positive RCL test result ● Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene ● New malignancy (T-cell & non T-cell), other than primary malignancy ● Progressive multifocal leukoencephalopathy (PML) ● Hepatitis B reactivation	● Intravenous Immunoglobulin

14.5 **Appendix 5**: Liver event and Laboratory trigger Definitions and Follow-up Requirements

14.5.1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	ALT or AST > 5 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBIL > 3 × 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*
If ALT or AST abnormal at baseline.	ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

[redacted]

14.5.2 Follow Up Requirements for Liver Laboratory Triggers - ALT, AST, TBL

ALT	TBL	Liver Symptoms	Actions
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• No change to study treatment • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If elevated at baseline: ALT > 2 x Baseline or > 300 U/L (whichever occurs first)			
If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• Interrupt study drug • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) for participants with Gillbert's syndrome: Doubling of direct bilirubin	None	• Interrupt study drug • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If elevated at baseline: ALT > 2 x baseline			

[redacted]

ALT	TBL	Liver Symptoms	Actions
or > 300 U/L (whichever occurs first)			• Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: **ALT > 3 x ULN**	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT > 2 x Baseline or > 300 U/L (whichever occurs first).			

14.6 **Append**ix 6: Specific Renal Alert Criteria and Actions and Event Follow-up

14.6.1 Specific Renal Alert Criteria and Actions

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

[redacted]

Renal Event	Actions
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

14.6.2 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]