NOVARTIS

Clinical Development

CTL019

Protocol CCTL019B2202 / NCT02435849

A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia

Document type	Amended Protocol Version
EUDRACT number	2013-003205-25
Version number	07 (Clean)
Development phase	II
Document status	Final
Release date	26-Oct-2020

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/SGPT
AML	Acute Myeloid Leukemia
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/SGOT
ATG	Anti-thymocyte globulin
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUC_{28d}	Area under the curve from day 0 to 28 days following infusion in the cellular kinetic profile
AUC_{84d}	Area under the curve from day 0 to 84 days following infusion in the cellular kinetic profile
AUMC	Area under the first moment curve
B-ALL	B cell lineage acute lymphoblastic leukemia
4-1 BB	type 2 transmembrane glycoprotein belonging to the TNF superfamily, expressed on activated T Lymphocytes
BCR-ABL	Philadelphia Chromosome
BiPAP	Bilateral Positive Airway Pressure
BM	Bone Marrow
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CAR	Chimeric Antigen Receptor
CBC	Complete Blood Count
CCGs	CRF Completion Guidelines
CD	Cluster of Differentiation
CD137	4-1BB costimulatory molecule
CFR	Code of Federal Regulations
CHP	Children's Hospital of Philadelphia
CI	Confidence Interval
CIF	Cumulative Incidence Function
CLL	Chronic Lymphocytic Leukemia
C_{max}	Maximum concentration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure

[redacted]

CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CRO	Contract Research Organization
CR_p	Complete remission with incomplete platelet recovery
CRP	C-Reactive Protein
CRS	Cytokine Release Syndrome
CSF	Cerebral Spinal Fluid
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte
CTL019 cells	CD 19 redirected autologous T cells (also called CART19 cells)
CVPF	Cell and Vaccine Production Facility
DILI	Drug-Induced Liver Injury
DOR	Duration of Remission
DLBCL	Diffuse Large B Cell Lymphoma
DLI	Donor Lymphocyte Infusion
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr Virus
EC	European Commission
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic Data Capture
EFS	Event Free Survival
EMA	European Medicines Agency
EOI	End of Induction
EOS	End of Study
EOT	End of Treatment and Primary Follow-Up
EQ-5D	European Quality of Life 5 Dimensions
EU	European Union
FAB	French-American-British
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FISH	Fluorescent *in situ* hybridization
FL	Follicular Lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor

[redacted]

GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GMP	Good Manufacturing Practice
GU	Genitourinary
GVHD	Graft versus Host Disease
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLT	High level term
HSCT	Hematopoietic Stem Cell Transplantation
IA	Interim Analysis
iAMP21	Intrachromosomal amplification of chromosome 21
IB	Investigator Brochure
ICH	International Conference on Harmonization
ICF	Informed Consent Form
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IL6R	Interleukin 6 receptor
IN	Investigator Notification
INR	International Normalized Ratio
IRC	Independent Review Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISBT	International Society of Blood Transfusion
IUD	Intrauterine Device
i.v.	Intravenous(ly)
IVIG	Intravenous Immunoglobulin
KM	Kaplan Meier
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
LP	Lumbar Puncture
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
LVSF	Left Ventricular Shortening Fraction
MAP	Master Analysis Plan
MAS	Macrophage Activation Syndrome
MCHC	Mean Corpuscular Hemoglobin Concentration

[redacted]

MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Authorities
MHC	Major Histocompatibility Complex
MLL	Mixed-Lineage Leukemia
MNC	Mononuclear Cells
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
MUGA	Multiple Uptake Gated Acquisition
MYC	A regulator gene located on chromosome 8 that is disregulated via translocations in Burkitt's lymphoma/leukemia
NCCN	National Comprehensive Cancer Network
NE	Norepinephrine Equivalent
NHL	non-Hodgkin’s lymphomas
NR	No Response
O_2	Oxygen
ORR	Overall Remission Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PCR	Polymerase Chain Reaction
PCR	Urine Protein-Creatinine Ratio
PD	Pharmacodynamics
PE	Physical examination
PedsQL	Pediatric Quality of Life questionnaire
pH	Hydrogen ion concentration; a measure of the acidity or basicity of an aqueous solution
Ph+	Philadelphia Chromosome Positive
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PPS	Per-Protocol Set
PR	Partial Remission
PRO	Patient Reported Outcomes
PT	Preferred Term
PT	Prothrombin Time
PT/INR	Prothrombin Time and International Normalized Ratio
qPCR	Quantitative Polymerase Chain Reaction
QoL	Quality of Life
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RCL	Replication Competent Lentivirus
RDC	Remote Data Capture

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REB	Research Ethics Board
RFS	Relapse Free Survival
r/r	Relapsed or refractory
SAE	Serious Adverse Event
SC	Steering Committee
scFv	Single chain Fv fragment of an antibody
SCID	Severe Combined Immunodeficiency
SCT	Stem Cell Transplantation
sIg	Surface Immunoglobulin
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Event
TBIL	Total Bilirubin
T_{max}	Time to peak concentration
TNF	Tumor Necrosis Factor
TLS	Tumor Lysis Syndrome
TCR	T Cell Receptor
TCR-zeta	Signaling domain found in the intracellular region of the TCR zeta, gamma and epsilon chains
ULN	Upper Limit of Normal
UPCC	University of Pennsylvania Cancer Center
US	United States
VASST	Vasopressin and Septic Shock Trial
V_H	Heavy Chain Variable Domain
V_L	Light Chain Variable Domain
VSV-G	Vesicular Stomatitis Virus, Glycoprotein
WBC	White Blood Cell
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
Cohort	A specific group of patients fulfilling protocol defined criteria
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; defined as the point at which a patient meets all inclusion/exclusion criteria, and after which the patient's apheresed product is received and accepted by the Novartis designated manufacturing facility.
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulations (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
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number	A unique identifying number assigned to each patient who enrolls in the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, and Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
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
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including active drug run-ins. 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.
Supportive treatment	Refers to any treatment required by the exposure to a study treatment
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer and does not allow any further collection of personal data

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Amendment 7 (26-Oct-2020)

Amendment rationale

All patients enrolled in the Main Cohort had either received CTL019 infusion or discontinued without receiving CTL019 prior to release of amendment 6; enrollment into the Main Cohort was completed at the time of protocol amendment 6 release. Amendment 6 was released on 21-Mar-2019 in the United States (US) only and introduced Cohort 1 (patients who are very high risk of first relapse) and Cohort 2 (patients who received CTL019 within 6 months post allogeneic hematopoietic stem cell transplantation).

The current protocol amendment 7 is implemented to:

- Terminate the enrollment into cohorts 1 and 2 in the US as of 15-Jun-2020. Patient enrollment has been low, in part due to the availability of alternative treatment options. One patient had been treated in Cohort 1 and no patient had been treated in Cohort 2 at the time of these cohorts' termination. After consulting with the study steering committee, and considering the very low recruitment, the decision has been made to terminate the enrollment as per the termination letter sent out to Investigators on 15-Jun-2020 and the notification sent to FDA on 26-Jun-2020. The decision to terminate Cohort 1 and Cohort 2 is not due to any new safety concern or safety signal associated with CTL019. Amendment 7 documents that the US only cohorts 1 and 2 will not complete enrollment, and the related planned analyses will not occur
- 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. Notably, this change in follow-up time has already been implemented at US sites with amendment 6, however, amendment 7 will be released to all participating sites globally to ensure compliance with the 12-month required follow-up of live births
- Add the requirement for urine or serum pregnancy testing at all scheduled study visits to align with standard CTL019 monitoring requirements
- Clarify the requirements for lab testing in the case of secondary malignancies to align with program standard language. Notably, this sampling requirement was introduced in amendment 6, however it is now being clarified to include RCL testing, and being implemented in all participating sites globally with amendment 7
- Specify that blood samples for RCL testing are banked beyond month 12, as long as all samples through Month 12 were negative

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.

1. Protocol Summary: Updated Purpose and Rationale, Primary Objectives, Secondary Objectives, Population, Data Analysis as per the changes introduced by the Protocol Amendment 7.
2. Section 2.1: Updated to include enrollment termination into Cohort 1 and Cohort 2.

[redacted]

3. Section 2.2: Updated to include enrollment termination into Cohort 1 and Cohort 2. Updated to clarify enrollment completion into Main Cohort at time of PA6 release.
4. Section 2.3: Updated to include enrollment termination into Cohort 1 and Cohort 2.
5. Section 2.6: Section revised to include pregnancy risks and contraception requirements as per the latest program safety language.
6. Table 3-1: Section updated to include enrollment termination into Cohort 1 and Cohort 2. Clarified that endpoints will only be presented as listings for patient in Cohort 1.
7. Section 4.1: Updated to include enrollment termination into Cohort 1 and Cohort 2. Updated to clarify enrollment completion into Main Cohort at time of PA6 release.
8. Section 4.2: Updated definition of end of study and follow-up for patient in Cohort 1.
9. Section 5.1: Updated to include enrollment termination into Cohort 1 and Cohort 2. Updated number of patients enrolled in study.
10. Section 5.2: Updated to clarify Protocol Amendment 6 inclusion criteria applicable to US sites only.
11 Section 6.1.1.2: Updated to include required serum pregnancy testing within 24 hours prior to infusion to align with the latest standard program safety language.
12. Section 6.2.4.3: Updated to clarify the requirements for lab testing in case of secondary malignancies including Replication-competent lentivirus (RCL) testing and storing of blood samples for potential RCL testing in future.
13. Table 7-1: Removed serum pregnancy test at M60 (EOT) visit for only Cohort 1 and Cohort 2. Updated to clarify serum pregnancy test will be collected for all WOCBP at EOT visit. Serum or urine pregnancy testing added to Visit Evaluation Schedule: treatment and primary follow-up phase (Day 28 to Month 54) per standard program safety language.
14. Table 7-2: Serum or urine pregnancy testing added to Visit Evaluation Schedule: secondary follow-up phase per standard program safety language. Updated to clarify serum pregnancy test will be collected for all WOCBP at EOT visit.
15. Section 7.1.3: Added serum or urine pregnancy test collection during post-infusion visits (Day 28 to Month 54) per standard program safety language. Also added banking of blood samples collected at Months 24 to 54 for potential future RCL testing.
16. Section 7.1.3.1: Added banking of blood samples for potential future RCL testing. Revised language to clarify serum pregnancy test will be performed on all WOCBP at M60 (EOT) visit.
17. Section 7.1.4: Added banking of blood samples for potential future RCL testing. Added serum or urine pregnancy testing per standard program safety language.
18. Section 7.1.6: Added banking of blood samples for potential future RCL testing.
19. Table 7-5: Updated urine and serum pregnancy testing requirement per standard program safety language.
20. Table 7-7: Added banking of blood samples for potential future RCL testing.
21. Table 7-12: Added banking of blood samples for potential future RCL testing.
22. Section 8.4: Added pregnancy testing per standard program safety language and deleted duplicate text.

23. Section 10: Section updated to include enrollment termination into Cohort 1 and Cohort 2 and to specify that listings will be presented for the single patient enrolled into Cohort 1.
24. Section 10.2: Section updated to specify analyses will be performed in Main Cohort and only listings will be presented in Cohort 1.
25. Section 10.3: Section updated to specify analyses will be performed in Main Cohort and only listings will be presented in Cohort 1.
26. Section 10.4: Updated to include enrollment termination into Cohort 1 and Cohort 2.
27. Section 10.4.2: Section updated to remove the primary efficacy analysis for Cohort 1 and Cohort 2. Specified that only listing will be presented in Cohort 1.
28. Section 10.4.4.1: Section revised to specify that subgroup analyses will be performed in Main Cohort.
29. Section 10.5.2.12: Section updated to remove Cohort 2 and to specify how the efficacy will be summarized in Cohort 1.
30. Section 10.5.3.10: Section updated to remove Cohort 2 and to specify how the safety will be reported for Cohort 1.
31. Section 10.5.4: Section revised to specify that analyses will be performed for Main Cohort only. Added that only listings will be presented for Cohort 1.
32. Section 10.6.1: Revised language to clarify additional exploratory assessment may be performed in Main Cohort.
33. Section 10.6.1.3: Revised to specify that basic tables, listings and figures will be updated for Main Cohort.
34. Section 10.6.2: Revised to specify that CTL019 product characteristics will be summarized in Main Cohort.
35. Section 10.6.3: Revised to specify that CRS and response to therapy will be listed for Main Cohort.
36. Section 10.6.4: Revised to specify that healthcare resource utilization will be summarized in Main Cohort.
37. Section 10.8: Revised to specify one patient enrolled into Cohort 1 and no patients were enrolled into Cohort 2.
38. Section 11.3: Added required program standard language for consenting pregnant female partners of male patients.
39. Editorial changes including minor deletions and additions are also made within this protocol amendment.

IRBs/IECs

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.

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Amendment 6 (21-Mar-2019)

Amendment rationale

At the time of the latest data cut-off (13-Apr-2018), 113 pediatric and young adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (ALL) were screened, and 97 were enrolled in the study and 45 patients are still ongoing in the study overall. At the time of data cutoff, enrollment was closed. All enrolled patients have either received CTL019 infusion or discontinued without receiving CTL019. All patients who received CTL019, have been followed for at least 3 months or have discontinued earlier.

With this clinical protocol amendment 6, approximately 20 additional patients will be screened in two additional cohorts to allow at least 15 additional patients to be treated with CTL019 manufactured from a certified manufacturing facilities participating for this study in each of the two cohorts.

At the Amendment 6, three cohort definitions are introduced:

- Main Cohort: all patients screened before protocol Amendment 6
- Cohort 1: patients who are very high risk at first relapse
- Cohort 2: patients who received CTL019 within 6 months post allogenic hematopoietic stem cell transplantation (allo-HSCT)

Target population (Cohort 1 and Cohort 2): To evaluate if CTL019 is effective in patients with very high risk B-ALL at first relapse, the protocol is being amended to add a cohort of at least 10 infused patients with either very high risk cytogenetic features (extreme hypodiploidy defined as fewer than 44 chromosomes and/or Deoxyribonucleic Acid (DNA) index less than 0.81 or t(17;19) with defined TCF3-HLF fusion) at diagnosis that experience a relapse or any patient with B-cell ALL that relapses ≤36 months of initial diagnosis and who has minimal residual disease (MRD) ≥0.01% at end of reinduction therapy (Cohort 1). Additionally, to investigate the feasibility and safety of administering CTL019 in patients with early relapse post HSCT, a second cohort of at least 5 infused patients will be added to this protocol to enroll patients that relapsed less than 6 months post allo-HSCT, regardless of the number of relapses (Cohort 2).

This recruitment will be limited only to the United States (US) sites.

ALL is most common malignancy of childhood (Childhood Blood Cancer Facts and Statistics, The Leukemia and Lymphoma Society website, 2018) and relapsed ALL is a leading cause of cancer death in children, adolescents and young adults. In patients up to 25 years with refractory or in second or greater relapse, CTL019 has shown the potential to be a definitive therapy, providing early, deep and durable remissions. Given the unprecedented responses in these difficult to treat patients, it has been hypothesized that CTL019 could be effective also in earlier lines of therapy in very high risk patients.

Current treatment protocols for ALL in children emphasize risk-based therapy in order to reduce toxicity in low risk patients while ensuring appropriate, more aggressive therapy for those with a high risk of relapse (Cooper at al 2015).

[redacted]

Very high risk ALL account for app. 8-10% of all B-ALL patients and remains a therapeutic challenge. Certain biologic and response factors designate patients to be in the very high risk group including those with extreme hypodiploidy (44 or fewer chromosomes and/or DNA index less than 0.81), t(9;22) Philadelphia chromosome rearrangement (BCR/ABL1), t(4;11) KMT2A (MLL) rearrangement, intrachromosomal amplification of chromosome 21 (iAMP21), those over 13 years of age in the United States, and/or failure to achieve complete remission (CR) at the end of induction (EOI) therapy (>5 percent lymphoblasts in day 28 bone marrow (BM) or the presence of MRD). In the past, this group of patients had overall a poor prognosis, but subsets of these patients can be successfully treated with aggressive chemotherapy, often in combination with hematopoietic stem cell transplant and / or targeted therapy (such as imatinib for Philadelphia Chromosome Positive (Ph+) ALL) with the rate of event-free survival at 5 years being 40% with standard chemotherapy regimens in this population (Pulsipher et al 2011).

Augmentation of therapy to include allogeneic stem-cell transplantation in first complete remission has been shown to improve disease-free survival for a subset of this patient population, but it is associated with higher treatment related morbidity. Several studies have reported that transplantation in first complete remission results in a 5-year disease-free survival of 55%-60% for patients with very-high risk ALL, including a comparative analysis of transplantation to chemotherapy alone which resulted in a 16% survival benefit at 5 years from transplant (Fagioli et al 2013, Balduzzi et al 2005, Satwani et al 2007). Despite improvements in survival with allogeneic stem-cell transplant, children with very-high risk ALL still have a 24% risk of relapse at 10 years compared with a 15% risk observed in standard-risk ALL patients (Fagioli et al 2013, Malempati et al 2007). Furthermore, the use of allogeneic stem-cell transplantation is less effective if patient remains MRD positive after intensive chemotherapy or if patient has certain biological features such as extreme hyplodiploidy. Minimal residual disease status in ALL has been shown to predict the risk of relapse, event free survival and overall survival (EFS and OS) when measured during and after induction therapy in both newly diagnosed and relapsed ALL (Borowitz 2015). For example, in a study assessing outcomes after re-induction chemotherapy for relapsed pediatric patients, at 5 years, EFS was 15% ± 6% in MRD positive patients while EFS was 56% ± 10% in MRD negative patients (Raetz and Bhatla, 2012).

Early relapse is one of the strongest predictor of survival (time of relapse from initial diagnosis) and patients who relapsed less than 18 months after diagnosis had poor outcome, with a 5-yr survival rate of approximately 21±1.8% (Nguyen at al, 2008). Leukemia. Patients with very high risk features tend to relapse rapidly after intensive chemotherapy, including post allogeneic HSCT.

The protocol safety language was updated to reflect the current Novartis standard safety measures. Main safety changes include updates to the highly effective contraceptive methods for women of childbearing potential (WOCBP) in the respective exclusion criterion, updates to the cytokine release syndrome (CRS) algorithm and CRS grading (Lee et al, 2014) based on the modified program standard language and Food and Drug Administration (FDA) feedback, addition of bio-sampling to follow-up on newly occurring cases of secondary malignancy, and management of drug induced liver injury in addition to liver and renal safety monitoring.

Given that enrollment of the main cohort was completed, no changes to inclusion/exclusion criteria were incorporated for the patients already enrolled and treated in the main cohort. However, according to Investigator's Brochure edition 07 (Released date 17 Oct 2018) the

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contraception requirement changed and for patients to be enrolled in Cohort 1 and Cohort 2 only exclusion 13 and 18 were retired and criterion 21 added, whereas all other exclusion criteria remained unchanged and are applicable. Collection of serum and peripheral blood for immunogenicity at month 24 from patients in Cohort 1 and Cohort 2 was added for longer follow up as per the request from Health Authorities. Leukapheresis assessment was added as part of this protocol amendment, as previously leukapheresis for this study was performed under the CTL019B2206 study. Lastly, the dosing for the Cohort 1 and Cohort 2 was determined as per the label information.

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.

1. List of abbreviations was updated.
2. Protocol Summary: Updated Purpose and Rationale, Primary Objectives, Key Secondary Objectives, Secondary Objectives, Population, Inclusion and Exclusion Criteria, Investigational and reference therapy, Data Analysis as per the changes introduced by the protocol amendment 6.
3. Section 1.2.1.2: Updated the clinical experience section with more recent clinical efficacy, safety, and cellular kinetics data
4. Section 2.1: Updated to include rationale and purpose of protocol amendment 6.
5. Section 2.2: Updated to introduce the definitions for the three cohorts, including introduction of the two newly added Cohorts 1 and 2.
6. Section 2.3: Revised text regarding the dose calculation for Cohort 1 and Cohort 2.
7. Section 3: Updated text stating that hypotheses testing for key secondary objectives are applicable for Main cohort only.
8. Table 3-1: Section updated to include primary objectives and endpoints for the newly added Cohort 2 and clarified that and the existing primary objectives and endpoints are applicable for Main Cohort and Cohort 1 as per Table 3-1.
9. Section 4.1: Section updated to include the description of the newly added Cohort 1 and Cohort 2.
10. Section 4.1.1: Section updated to include criteria to be followed prior to leukapheresis collection, requirement for sample sentinel vial collection as per the latest Investigational Leukapheresis, Cryopreservation & Scheduling Manual
11. Section 5.1: Updated with the patient population information to be included in Cohort 1 and Cohort 2,
12. Section 5.2: Section revised to remove the existing inclusion criteria 1 and 6 (which were applicable for the screening of patients into Main Cohort only) and to add inclusion criteria 11 and 12 which are applicable for the newly added Cohort 1 and Cohort 2
13. Section 5.3: Section revised to remove the existing exclusion criteria 13 and 18 (which were applicable for the screening of patients into Main Cohort only) and to add exclusion criteria 19, 20, and 21 which are applicable for the newly added Cohort 1 and Cohort 2.
14. Section 6.1: Study Treatment section was updated with the dosing information for patients in Cohort 1 and Cohort 2.

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15. Section 6.1.3: Treatment for cytokine release section has been updated with the Lee grading system and management algorithm based on the latest program standard language and FDA feedback.
16. Section 6.2.4.2: General toxicity management considerations section was revised by removing the language specific to Japanese patients. Tables 6-1 and 6-2 have been added for the CRS management algorithm and grading as per the Lee. CRS management algorithm has been modified at the program level based on FDA feedback.
17. Section 6.2.4.3: New or secondary malignancies toxicity language was updated as per the latest program safety language.
18. Section 6.3.2: Liver safety monitoring language was updated and added sub-sections to include renal safety monitoring details as per the latest program safety language.
19. Section 6.5.3.2 – Disposal information of CTL019 was previously misreported here therefore deleted from this section.
20. Section 6.5.4 - Disposal and destruction section was updated
21. Tables 7-1 and 7-2: Primary follow-up visit evaluation schedule updated with addition of leukapheresis/apheresis, leukapheresis/apheresis pre-evaluation and acceptance assessments at screening, removal of the serum or urine pregnancy test at pre-infusion, addition of the serum pregnancy test at lymphodepleting chemotherapy, pre-infusion visits, End of Treatment (EOT) visits, addition of the EOI local MRD assessment in bone marrow aspirate at screening, addition of the menstrual status assessment at screening, addition of the (M24) collection of the immunogenicity sample in serum and peripheral blood during the treatment and primary follow-up and secondary follow-up visits.
22. Section 7.1.1: Updated to include the EOI MRD local assessment.
23. Section 7.1.3.2: Criteria for premature patient withdrawal form Treatment and Primary Follow-up Phase were updated as per latest Novartis standard language.
24. Section 7.2.3: Updated visit assessments based on Table 7-1 and Table 7-2 with Immunogenicity (Serum and Peripheral blood) collection at M24 as per request from Health Authority for a longer follow-up.
25. Section 8.1.2: Section updated with the guidelines on reporting the underlying malignancies as per the latest program safety language.
26. Section 8.4: updated to reflect pregnancy reporting as per the latest program safety language
27. Section 10: Section updated to include details on newly added Cohort 1 and Cohort 2 and to specify which statistical methods and what type of data analysis is applicable for each.
28. Section 10.2: Section updated to remove Chemorefractory definition and to specify that this section is applicable for Main Cohort, Cohort1, and Cohort 2.
29. Section 10.3: Updated to specify that this section is applicable for Main Cohort, Cohort1, and Cohort 2
30. Section 10.4: Section updated to clarify which objectives are applicable for Main Cohort, Cohort 1, and Cohort 2
31. Section 10.4.1: Updated to add primary efficacy endpoint for Cohort 1 and primary safety endpoints for Cohort 2

[redacted]

32. Section 10.4.2: Section updated to clarify which method of analysis will be used for Main Cohort, Cohort1, and Cohort 2
33. Section 10.4.4: Section updated to clarify which supportive analyses will be used for Main Cohort.
34. Section 10.5: Section updated to include section 10.5.1 to specify that hypothesis testing of key secondary end-points will only be performed for patients in Main cohort
35. Section 10.5.2.12: Section added to specify how the efficacy will be summarized in Cohort 1 and Cohort 2.
36. Section 10.5.3.10: Section added to specify how the safety will be reported for Cohort 1 and Cohort 2.
37. Section 10.8: Section updated to include details on the sample size calculations for the Cohort 1 and Cohort 2.
38. Section 10.9: Section header updated to clarify that the key secondary objectives are only applicable for Main Cohort.
39. Section 13: References were updated
40. Section 14.3: Appendix 3 updated with any non-serious Adverse Events (AEs) ≥ Grade 3 or condition the investigator believes may have a reasonable relationship to CTL019 therapy and any Serious Adverse Events (SAEs) irrespective of grade in Primary Follow up Phase after M12.
41. Section 14.7: Appendix 7 added latest program safety language
42. Section 14.8: Appendix 8 added latest program safety language
43. Editorial changes including minor deletions and additions are also made within this protocol amendment.

IRBs/IECs

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

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 5 (04-Apr-2017)

Amendment rationale

At the time of this protocol amendment, 26 sites have been initiated and enrollment was closed with 92 patients enrolled globally, and 75 patients infused with CTL019. The primary endpoint and all three key secondary endpoints were met at the interim analysis conducted with the first 50 infused patients who had completed at least 3 months of follow-up or discontinued earlier. The analyses of these endpoints were updated after all 63 patients who received CTL019 from US manufacturing facility had been followed for at least 3 months or discontinued earlier.

In order to support the development of CTL019 in Japan, at least 5 Japanese patients were to be infused with CTL019. The target number of Japanese patients infused with CTL019 was set after consultation with PMDA. As of enrollment closure on 01-Feb-2017, 2 patients from Japan have been infused with CTL019, both from US manufacturing facility. Therefore the enrollment will be re-opened for additional patients in Japan. Approximately 5 additional Japanese patients will be screened to allow at least 3 additional patients to be infused with CTL019 manufactured from the US facility (total 5 Japanese patients infused). Sponsor approval will be required to screen more than 5 patients, which is based on target number of infused patients.

While tocilizumab is available in Japan, siltuximab or other alternative anti-IL6 drugs specified in the Cytokine Release Syndrome (CRS) management algorithm are not available. Therefore, the CRS management algorithm has been modified to accommodate changes applicable for Japan specifically to address the availability of tocilizumab as the only anti-IL-6. To date the experience with siltuximab in patients with sub-optimal responses to tocilizumab is still limited. Patients with CRS have been adequately managed utilizing tocilizumab (up to three doses) along with steroids and with avoidance of TNF antagonists. The Japan CRS algorithm now establishes 6 lines of management including required 3rd line steroid treatment, three doses of tocilizumab and the avoidance of TNF antagonists. Therefore, the Japan CRS algorithm provides adequate management and guidelines for CTL019 related CRS.

Contraception language was changed for clarity.

Additional safety reporting clarification, is added in patients in secondary follow-up phase receiving additional anti-cancer therapies (e.g. stem cell transplant, chemotherapy) after CTL019 infusion. The updated safety reporting requires any severe adverse event or condition the investigator believes may have a reasonable relationship to investigational CTL019 therapy to be reported in the data base.

Guidelines for use of fibrinogen concentrate in CTL019-associated coagulopathy with hypofibrinogenemia for the EU and Japan have been included in the appendices as these guidelines were previously distributed to the sites.

Changes to Protocol

1. List of abbreviations: Updated
2. Amendment 4 Rationale: Corrected reference typo
3. Protocol Summary: Updated population.

[redacted]

4. Section 1.2.1.2: Added reference to Figure 6-2.
5. Section 2.2: Sample size updated.
6. Section 4.1: Updated with additional enrollment for Japan
7. Section 5.1: Sample size updated to include additional enrollment in Japan
8. Section 5.3: Updated contraception criteria.
9. Section 6.1.3: Updated treatment for cytokine release syndrome for Japan only.
10. Section 6.2.4.2: Updated cytokine release syndrome section to include number of patients on CTL019B2202 treated with siltuximab. Added cytokine release syndrome section for Japan only to address absence of siltuximab in Japan and added reference to Japan CRS management algorithm. Updated section on B-cell depletion with guidance on vaccines.
11. Figure 6-2: Added Japan CRS management algorithm.
12. Section 7.1.3.3: Updated section.
13. Section 7.1.4.1: Updated section
14. Section 7.2.3: Added statement to clarify CTL019 PK and cellular kinetics.
15. Section 8.4: Updated contraception requirements for male participants and male partners. Updated Novartis safety information. Added instructions for pregnancy outcomes for female partners.
16. Section 10.4.4.1: Added Japanese patient sub-group analysis.
17. Section 11.5: Updated section with clinical result reporting and authorship guidelines.
18. Section 14.4: Updated Appendix 4
19. Section 14.5: Added Appendix 5
20. Section 14.6: Added Appendix 6

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/EC approval prior to implementation only in Japan. In addition, if 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 amended protocol.

Amendment 4 (14-Jun-2016)

Amendment rationale

At the time of this protocol amendment, 26 sites have been initiated, 76 patients have been enrolled globally, and 54 patients have been infused with CTL019 manufactured in the US.

In published data (Grupp 2013, Maude 2014) with CTL019 and in current clinical trial experience, all complete remissions in pediatric ALL have been achieved no later than Month 3 post-CTL019 infusion. Discussions with the FDA have indicated that a 3 month follow-up may be adequate for initial submission to the FDA to support the marketing authorization of CTL019 in the US.

[redacted]

Therefore, the post-infusion follow-up duration for assessing the primary objective of ORR for each patient has been changed from 6 months to 3 months. Patients will continue to be follow-up for efficacy assessments according to Amendment 3 (No change in this regard in Amendment 4).

Novartis plans to use the CTL019 manufacturing process at the Fraunhofer Institut für Zelltherapy, Leipzig, Germany, a CMO to establish a second manufacturing site. Therefore, an additional cohort of patients (up to 14) will be enrolled from the EU to treat them with CTL019 manufactured at the facility in Europe (Fraunhofer Institute) has been included to assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CTL019 manufactured by Fraunhofer Institute, and to assess clinical product comparability between the US and EU manufacturing facilities. To support the analysis, an additional secondary endpoint has been introduced. Therefore, the approximate total number of enrolled patients has been revised to 95 patients.

Two additional key secondary endpoints have been incorporated to allow evaluation of ORR and MRD-negative ORR only for CTL019 manufactured at the US manufacturing facility.

An interim analysis has been planned to be conducted with the first 50 CTL019 infused patients after they have either completed 3 months of follow-up or discontinued earlier.

The schedule of immunogenicity collections has been reduced and limited to 12 months post-CTL019 infusion. This reduced collection is based upon a single CTL019 infusion schedule versus chronic study treatment dosing where in the former an extended sample collection is not informative due to the lack of repeated dosing.

A minimum of one year follow-up at the treating investigational site is strongly recommended with remote follow-up as a possibility beyond this one year periods for the following reasons:

- Relapse patterns and kinetics of relapsed/refractory pediatric ALL patients (majority of relapses following CTL019 occur within one year)
- Relapse and survival in this population can be adequately collected by the referring pediatric oncologist
- Treatment schedule is a single dose infusion with limited incentive to return to a treatment site
- Alignment with FDA

A subgroup analysis has been added for patients with Down Syndrome given their known increased treatment related ALL morbidity and mortality rates. Because of increased risk, stem cell transplant is often not recommended in this population. Therefore, the experience with CTL019 in this rare population may address this unmet medical need.

The modified data capture for concomitant medications has been clarified to ensure data capture of blood products related to a reportable AE or SAE which assists analysis of the overall CTL019 safety profile.

IRB/IEC

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

[redacted]

The changes described in this amended protocol require IRB/EC approval prior to implementation. In addition, if 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 amended protocol.

Changes to Protocol

1. Section 2.2: Sample size updated.
2. Table 3-1: Updated primary, key secondary, and other secondary objectives/endpoints
3. Section 4.1: Updated with additional enrollment for manufacturing from Fraunhofer Institute
4. Section 5.1: Sample size updated to include patients manufactured from Fraunhofer Institute
5. Section 6.1.1.1: Section updated with clarifications
6. Table 6-1: Penn grading scale for CRS Grade 3 updated to include fibrinogen concentrate
7. Table 7-1: Updated with clarifications and revision to immunogenicity collections
8. Table 7-2: Updated with clarifications and addition of immunogenicity collections
9. Section 7.1.3: Updated visit assessments based on Table 7-1
10. Section 7.1.3.2: Section updated to include importance of return to investigational site within first year post-infusion
11. Section 7.1.4: Section updated with clarifications
12. Section 7.1.5: Section updated with clarifications
13. Table 7-5: Correction of errors
14. Section 7.2.3: Tables updated to include unscheduled collection at relapse
15. Table 7-13 and Table 7-14: Updated immunogenicity sample collection schedule per Table 7-1 and Table 7-2
16. Table 7-15 and Table 7-16: Updated to include collection plan for additional doses of tocilizumab and siltuximab
17. Table 7-17: Updated to include unscheduled collection at relapse
18. Section 7.2.5: Section updated.
19. Section 10: Entire section updated to capture analysis plans for updated/new protocol objectives at interim and primary analysis, addition of down syndrome subgroup, and better define prior response status at baseline
20. Table 10-3: Clarification on AESI group team
21. Appendix 3: Updated to include clarification on blood product reporting in pre-treatment and treatment period

[redacted]

Amendment 3 (13-Apr-2016)

Amendment rationale

At the time of this protocol amendment, 26 sites have been initiated, 69 patients have been enrolled, and 41 patients have been infused with CTL019.

The protocol is being amended to institute updates on safety, manufacturing of CTL019 product, patient management, and eligibility criteria based on experiences from ongoing trials and recommendations from Health Authorities, Study Steering Committee and Data Monitoring Committee.

Key changes include:

1. Clinical experience (Section 1.2.1.2) updated to include more recent data and outcome of first 3 patient run-in data from this trial.
2. Target CTL019 dose range for patients > 50 kg has been expanded, and allowable infused dose ranges have been defined.

   The allowable infused cell dose range of CTL019 transduced cells have been defined as 0.2 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 autologous CTL019 transduced viable T cells (for patients > 50 kg) based on updated manufacturing cell dose release criteria. CTL019 products below these minimum transduced cell doses will not be released for infusion.

   The target cell dose range for purposes of trial analysis remains unchanged for patients ≤ 50 kg and for patients > 50 kg a range has also now been specified (1 to 2.5 x 10^8 transduced CTL019 cells

   The statistical plan for the per protocol dose analysis for 2 to 5 x 10^6 CTL019 transduced viable T cells per kg body weight is unchanged, and the 1 to 2.5 x 10^8 CTL019 transduced viable T cells is now provided as a range. At the time of this amendment, no patient has received a dose < 0.2 x 10^6 CTL019 transduced viable T cells. This change is considered to have a minimal impact on the per protocol dose statistical analysis.
3. Method of bone marrow MRD analysis in the key secondary endpoint was changed from qPCR to flow cytometry due to suboptimal sensitivity of the qPCR assay. Analysis by qPCR will be an exploratory endpoint.
4. Cellular immunogenicity analysis will be changed to an exploratory endpoint because the assay is not fully validated.
5. Cell counts for leukapheresis collection have further been clarified to better inform investigators and optimize collection for manufacturing, in addition to the collection of sentinel vials to better characterize apheresis product at the manufacturing site.
6. Extended the allowance of more than 10 patients ≥ 18 years old after Sponsor approval
7. ECHO/MUGA screening assessment may be performed within 7 days of screening.
8. IUD in place prior to consent may remain in place.
9. Medication restrictions updated. Use of steroids for non-GVHD and GVHD indications has been further clarified. Time windows have been revised to accommodate the

[redacted]

respective medication half-lives and dose, and expected time to toxicity resolution (i.e. prior radiotherapy).

- Clarification that systemic steroids have 72 hour restriction for non-GVHD indications
- Systemic steroids added to GVHD therapy restrictions
- Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion
- Hydroxyurea removed from restriction within 1 week prior to CTL019 infusion as this has been changed to 72 hours for this medication
- Methotrexate ≥ 25 mg/m^2 added to 2 week chemotherapy restriction
- Non-CNS and CNS radiotherapy added with time windows
- Anti T-cell antibodies prohibited within 8 weeks prior to CTL019 infusion

10. Due to the continued experience with CTL019 in over 100 patients with pediatric r/r ALL, the study no longer requires pausing the study for certain life threatening events and deaths suspected to be related to CTL019 therapy.
11. CRS algorithm and management updated with additional details to support trial investigators on appropriate CRS management.
    - Included recommended time intervals between subsequent doses of steroids and anti-cytokine therapies based on cumulative experience in 3 pediatric r/r ALL trials.
    - Added siltuximab within the CRS algorithm to be given following the 2nd dose of tocilizumab due to encouraging experience to date with this anti-cytokine therapy in pediatric and adult ALL patients.
    - Recommended that TNF antagonists not be used for CTL019 associated CRS because lack of activity seen to date and the concerns about their immunosuppressive effects.
12. Secondary follow-up phase revised to allow for remote visits and abbreviated AE/concomitant medication collection in order to maximize patient data collection post CTL019 infusion in non-responding patients and in patients undergoing further anti-tumor therapy to meet health authority requirements on cell and gene therapy trials.
13. AESI profile updated based on most current CTL019 safety profile
14. Pediatric ALL efficacy guidelines have been updated to further address certain areas of ambiguity for response assessments involving bone marrow biopsy or aspirate, peripheral blood, and timing of baseline assessments.
    - Trilineage Hematopoiesis (TLH) was removed as one of the components of CR definition in the bone marrow: ALL NCCN criteria do list this as a recommended bone marrow component for response. However, exact criteria for bone marrow TLH are not well established and potentially poorly reproducible. This can alternately be supported, in a reproducible and quantitative manner, by the use of peripheral blood platelet and neutrophil minimum values in the absence of transfusion of these blood components.
    - Changes and rationale of other tumor response elements are listed in Appendix 14.1 document history.

[redacted]

15. Exploratory objective is to correlate the relationship between CRS and clinical tumor response. Since CRS typically occurs by Day 28 and all tumor responses noted to date occurred by Day 28, it is justified to use the same time point for these two correlates.

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/EC approval prior to implementation. In addition, if 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 amended protocol.

Changes to Protocol

1. Section 1.2.1: Correction of typographical error
2. Section 1.2.1.2: Updated with more recent data.
3. Table 1-1: Table removed and reader directed to most current Investigator Brochure
4. Section 2.2: Enrollment numbers corrected.
5. Section 2.3: Target dose updated for patients > 50 kg updated
6. Section 2.3.1: Section added to include allowable infused cell dose range
7. Section 2.6: Added to include short description of risks and benefits
8. Table 3-1: Update to key secondary, other secondary, and exploratory endpoints.
9. Section 4.1.1: Section updated to include ALC and CD3 counts for leukapheresis collection and requirement for sample sentinel vials
10. Section 5.1: Updated to include clarity on patients ≥ 18 years of age
11. Section 5.2: Added window within screening for ECHO/MUGA assessments
12. Section 5.3: Updated contraception and concomitant medication criteria.
13. Section 6.1: Updated with new target and allowable infused cell dose ranges
14. Section 6.1.1.1: Clarification regarding use of alternative LD chemo regimen
15. Section 6.1.1.2: Updated to require influenza treatment be administered per label, updated concomitant medication restrictions, and added requirement of siltuximab on site within 24 hours of infusion per new CRS algorithm
16. Section 6.1.3: Title updated and clarifications added regarding CRS management
17. Section 6.2.3.3: Section removed
18. Section 6.2.4.1: Clarifications added
19. Section 6.2.4.2: CRS section updated to include details around cardiac monitoring, coagulopathy, and neurotoxicity
20. Figure 6-1: CRS management algorithm updated for more optimal CRS management
21. Figure 6-2: Figure removed
22. Section 6.2.4.3: Hepatitis B reactivation updated and new or secondary malignances toxicity added
23. Section 6.2.6: Added reference to Appendix 3: CTL019 Modified Data Reporting

[redacted]

24. Section 6.2.7: Updated prohibited concomitant medication criteria
25. Section 6.3: Added section and relevant sub-sections to include liver safety monitoring details
26. Section 6.4.1: Clarifications added
27. Section 6.5: Clarifications added
28. Section 6.5.1: Updated with new CTL019 dose ranges
29. Section 6.5.2: Minor updates added
30. Section 6.5.3.1: Clarification added
31. Table 7-1: Primary follow-up visit evaluation schedule updated
32. Table 7-2: Secondary follow-up visit evaluation schedule updated
33. Section 7.1.1: Section updated
34. Section 7.1.1.2: Title and section updated
35. Section 7.1.2: Section updated
36. Section 7.1.3: Section updated
37. Section 7.1.4: Section updated to include new secondary follow-up assessment schedule and details. AE and concomitant medication reporting details added
38. Section 7.2.2.4: Section updated to clarify tanner staging only for patients < 18 years old
39. Section 7.2.2.5: Section updated
40. Table 7-5: Local laboratory collections updated
41. Table 7-6: Central laboratory collections updated
42. Table 7-12: Table added to account for CTL019 transgene persistence during secondary follow-up phase
43. Section 7.2.4: Clarifications added
44. Section 7.2.5: New section added
45. Section 7.2.7.3: Clarifications added regarding translations and completion of questionnaires
46. Section 8.1.2: Section updated
47. Section 8.2.2: Section updated
48. Section 8.4: Section updated with new contraception and pregnancy language
49. Section 9.3: Updated to include manufacturing facility data entry
50. Section 9.4: Updated to include manufacturing facility data
51. Section 10.1.5: Section updated
52. Section 10.2: Section updated
53. Table 10-1: Updated according to efficacy guideline revisions
54. Section 10.4.4.1: Section updated
55. Section 10.5.1.1: Section updated
56. Section 10.5.2.3: Section updated
57. Section 10.5.2.10: Section updated
58. Section 10.5.3.2: AESI updates
59. Section 10.5.3.4: Section updated

[redacted]

60. Table 10-3: AESI terms updated
61. Section 10.5.3.7: Section updated
62. Section 10.5.3.9: Section updated
63. Table 10-4: PK parameters updated
64. Section 11.7: Clarification on confidentiality added
65. Section 13: References updated
66. Section 14.1: Appendix 1 updated with newest efficacy evaluation guidelines
67. Section 14.3: Appendix 3 added
68. Section 14.4: Appendix 4 added

Amendment 2

Amendment rationale

At the time of this protocol amendment, 1 site has been initiated, 3 patients have been enrolled, and 1 patient has been treated.

The protocol is being amended to ensure full alignment with the agreed binding measures detailed in the Pediatric Investigation Plan (PIP) opinion of the Paediatric Committee of the European Medicines Agency, issued on 20 March 2015 and to address recommendations from EMA Scientific Advice letter on 25 April 2014.

Key changes include:

1. The full analysis set should include at least 50 patients < 18 years (of which 10 patients are < 10 years old). The total number of enrolled patients has been increased accordingly to approximately 78 patients to be enrolled.
2. Elevation from secondary to key secondary endpoint for MRD by PCR based on its relevance as a surrogate marker correlated with clinical benefit in pediatric ALL. The sample size outlined above will provide 85 % to 91 % power to reject null hypothesis that percentage of patients with BOR of CR or CRi and MRD negative bone marrow <15% depending on the actual total number of patients infused with CTL019.
3. Elevation from exploratory endpoints to secondary endpoints relating to CRS, safety monitoring, and PROs
4. Addition of secondary objective: Derivation of a score to predict cytokine release syndrome
5. Day 28 tumor assessment window changed from +/- 7 days to +/- 4 days
6. Additional analyses have been included to assess the response at Day 28 +/- 4 days, impact of baseline tumor burden on response, etc.

In addition, other changes have been instituted for purposes of safety, clarity and feasibility based on experiences from ongoing trials as outlined below. Key changes include:

1. Clarifications to more accurately define the term “refractory ALL” in inclusion criteria #1. The two refractory populations now defined have equally poor prognosis at study enrollment and are not expected to negatively impact the population homogeneity.
2. Clarifications on influenza testing based on regions and seasonal variations

[redacted]

3. Extension of healthcare resource utilization collection visits
4. Clarifications on safety reporting and apheresis collections
5. Removal of PedsQL questionnaire collection in children ages 5-7

Changes to Protocol

1. Section 1.1: Correction of typographical errors
2. Section 1.2.1: Reference added
3. Table 1-1: Clarity added for patient population on the trials
4. Section 1.2.1.2: Clarification on correlation between administration of tocilizumab and CTL019 cell expansion
5. Section 2.1: References added
6. Section 2.3: Added “viable T” to dose
7. Table 3-1: Objectives and endpoints updated to include key secondary objective, addition of other secondary objectives, as well as shifting of exploratory objectives to secondary objectives.
8. Section 4.1.1: Clarity on guidelines for optimal apheresis collection
9. Section 4.1.1: Clarity on use of CTL019 manufactured cells if GVHD experienced after collection of apheresis product
10. Section 5.1: Patient population increased to approximately 78 patients enrolled, at least 50 infused patients < 18 years (at least 10 of which < 10 years)
11. Section 5.2: Clarification on the definition of refractory ALL added to criteria # 1
12. Section 5.3: Criteria # 10 retired and replaced with criteria # 15 with additional Anti T-cell therapy guidance
13. Section 6.1.1.2: Clarifications on influenza testing based on regions and seasonal variations. Anti T-cell Therapy details added. The number of tocilizumab doses required on site prior to CTL019 infusion changed to two doses. Clarification on which specific manual referenced. Guidance on monitoring of patient temperature added.
14. Section 6.1.3: Number of tocilizumab doses required on site prior to CTL019 infusion changed to two doses.
15. Section 6.2.4.2: CRS management algorithm to be followed by investigators
16. Section 6.2.6: Modified concomitant medication reporting better defined; clarification on concomitant medication recording prior to screening
17. Section 6.2.7: Anti T-cell Therapy guidance added
18. Section 6.4: Clarification on which specific manual referenced, and changed “the person” to “personnel” to ensure alignment with manuals
19. Section 6.4.2: Clarification on which specific manual referenced
20. Section 6.4.3: Clarification on which specific manuals referenced
21. Section 6.4.3.2: Clarification on which specific manual referenced
22. Section 6.4.4: Clarification on which specific manuals referenced
23. Table 7-1: Day 28 window changed from +/- 7 days to +/- 4 days
24. Table 7-1: Hospitalization status collection changed from Day 1 to screening

[redacted]

25. Table 7-1: MRD assessment by bone marrow aspirate by flow cytometry to include T cell counts
26. Table 7-1: MRD assessment in bone marrow aspirate by qPCR added for clarity
27. Table 7-1: “Aspirate” added to lymph node or other involved tissue assessment
28. Table 7-1: If bone marrow unavailable for genomic analysis, peripheral blood can be used if tumor cells are present in the peripheral blood at relapse
29. Section 7.1.1: “at the time of screening” added to performance status assessment; T cell numbers added to bone marrow aspirate and biopsy and peripheral blood flow cytometry
30. Section 7.1.2: Collection time point of PROs clarified at enrollment; Clarification on influenza testing based on regions and seasonal variations
31. Section 7.1.3: T cells added for flow cytometry; Day 28 window changed to +- 4 days; “aspirate” added to lymph node assessment
32. Section 7.1.3.3: If bone marrow aspirate is not available, peripheral blood can be used if tumor cells are present in the peripheral blood at relapse
33. Section 7.1.4: T cells added for flow cytometry
34. Table 7-3: T cells added for flow cytometry of peripheral blood
35. Section 7.2.2: Further Tanner staging not required if patient classified as Tanner stage 5
36. Section 7.2.2.4.1: Male tanner stage 5 (pubic hair) corrected
37. Table 7-5: CD4 and CD8 added to T cell levels
38. Table 7-6: CD4 and CD8 added to T cell levels
39. Section 7.2.3: Day 28 window changed to +/- 4 days for all applicable tables
40. Table 7-16: Day 28 window changed to +/- 4 days
41. Section 7.2.5: Hospitalization status collection changed from Day 1 to screening
42. Section 7.2.6: Collection time point of PROs clarified at enrollment; instruction that child should face away from the parent removed
43. Section 7.2.6.1: Removal of PedsQL Young Child for ages 5-7
44. Section 7.2.6.2: Clarifications and corrections made, and reference to PRO administration guidelines added
45. Section 8.1.2: Clarification added on adverse event reporting while patient simultaneously enrolled on CTL019B2206
46. Section 8.2.2: Clarification added on serious adverse event reporting while patient simultaneously enrolled on CTL019B2206
47. Section 8.4: “salpingotomy” corrected to “bilateral salpingectomy”
48. Section 10: Section updated with new population details
49. Section 10.1: Section updated based on new population
50. Section 10.2: Primary refractory definition clarified
51. Section 10.4 and subsections: Statistical analysis updates based on changes implemented in protocol
52. Section 10.5.1.1: Section updated
53. Section 10.5.2.2: Section updated
54. Section 10.5.2.4: Section removed (CR or CRi with MRD negative bone marrow)

[redacted]

55. Section 10.5.2.7: Section added
56. Section 10.5.2.8: Section added
57. Section 10.5.2.9: Section added
58. Section 10.5.2.10: Section added
59. Section 10.5.3.5: Section added
60. Section 10.5.3.6: Section added
61. Section 10.5.3.7: Section added
62. Section 10.5.3.9: Section updated
63. Section 10.5.4: Section update
64. Table 10-4: Table updated with more details
65. Section 10.6.1: Section updated
66. Section 10.6.1.3: Section updated
67. Section 10.6.4: Patient reported outcome section removed and moved to Section 10.5.2.7
68. Section 10.8: Section updated
69. Section 10.9: Section updated to include key secondary endpoint analysis
70. Section 13: References added

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/EC approval prior to implementation. In addition, if 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 amended protocol.

Amendment 1

Amendment rationale

At the time of this protocol amendment, no sites have been initiated and first patient first visit (FPFV) has not occurred. All sites are to be initiated with the current protocol amendment.

The protocol is being amended in order to include additional safety information and includes Health Authority feedback regarding reporting of SAEs including CRS and deaths, follow-up time required after a live birth, and revision of the inclusion criteria regarding the age at screening and local leukapheresis criteria.

Patient Report Outcomes (PROs) have been added to assess the patient's health related quality of life and patient function following cellular therapy.

The window between informed consent and CTL019 infusion has been widened from 8 weeks to 16 weeks. From ongoing phase I clinical trial experience in over 40 patients with r/r pediatric ALL receiving CTL019 therapy, the interval from ICF to CTL019 infusion has been up to 19 weeks. Pediatric patients exceeding a 12 week interval from ICF to infusion in this ongoing phase I trial have shown similar outcomes with CTL019 with no additional safety concerns

[redacted]

compared to those patients with a time window less than 12 weeks. This widened time interval from 8 to 16 weeks is necessary to complete all of the following: patient screening, ongoing stabilization of r/r leukemic disease with salvage chemotherapy and the management of typical complications resulting from salvage chemotherapy and/or the prolonged cytopenias related to the disease itself (e.g. infections requiring hospitalization), manufacturing of the cell therapy product and administration of the LD chemotherapy. Apheresis could potentially also occur during this interval.

Additional PK and cytokine sample time points were added to better define cell expansion and CRS, as well as the addition of exploratory endpoints that did not impact total sample collection requirements.

Unnecessary testing of CMV and EBV at screening as per current guidelines for autologous blood product therapy has been removed.

In addition, other changes have been instituted for purposes of safety, clarity and feasibility based on experiences from ongoing trials as outlined below.

Changes to the protocol

1. Section 1.2.1.2: Updated clinical experience section with currently available data.
2. Table 1-2: Removed and replaced with summary text
3. Table 2-1: Removed and replaced with summary text
4. Table 3-1: Updated secondary endpoints and added exploratory endpoints.
5. Figure 4-1: Study design diagram updated with extended windows from ICF to CTL019 infusion.
6. Section 4.1.1: Clarifications around apheresis product and exploratory endpoint language added.
7. Section 5.2: Changed age at screening from age 2 at initial diagnosis to age 3 at screening. Added an additional inclusion criteria to confirm patient meets local institutional criteria for leukapheresis.
8. Section 5.3: Clarifications to testing time windows and chemotherapy in exclusion criteria.
9. Section 6.1.1.1: Clarification on timing of lymphodepleting chemotherapy before CTL019 infusion.
10. Section 6.1.1.2: Clarifications on patient safety and requirements prior to CTL019 infusion. Vital signs follow-up post CTL019 infusion updated in line with data from ongoing trials.
11. Section 6.1.3: Clarifications on recording of rescue medications in the clinical database.
12. Figure 6-1: CRF Management Algorithm updated based on experiences from ongoing trials.
13. Table 6-2: Adjustment of vasopressor doses corrected by weight
14. Sections 6.2.4.2 & 6.2.4.3: Safety information added based on most current IB.
15. Section 6.2.6: Clarification on administration of granulocyte colony stimulating factor (G-CSF).
16. Section 6.2.7: Clarifications added.

[redacted]

17. Section 6.3.1: Re-screening language removed and better delineation of pre-infusion requirements have been included
18. Table 7-1: Primary Follow-up VES updated with new time points, clarifications, updated windows, addition and removal of assessments, and updates to table references.
19. Table 7-2: Secondary Follow-up VES updated with clarifications and additional assessments.
20. Section 7.1.1: Clarifications made throughout section impacting patient safety.
21. Section 7.1.1.1: Removed section due to widened window between ICF and CTL019 infusion. Screening procedures requiring repeat have been incorporated into other sections of the protocol.
22. Section 7.1.1.2: Reference to an enrollment form has been removed. Error in previous version.
23. Section 7.1.2: Section updated with new visit windows and clarifications for patient safety.
24. Section 7.1.3: Section updated with new visit windows and clarifications for patient safety.
25. Section 7.1.3.3: Section updated for clarification.
26. Section 7.1.4: Section updated for clarification.
27. Section 7.1.4.1: Section updated for clarification on research results and biological samples.
28. Table 7-3: Table updated for clarification.
29. Section 7.2.2.4: Tanner staging guidelines for male genitalia and public hair stages and female breast stages and public hair stages added for clarity.
30. Section 7.2.5: Added resource utilization to capture hospitalizations
31. Section 7.2.6: Added patient reported outcomes
32. Table 7-5: Table updated for clarification.
33. Table 7-6: Table updated for clarification
34. Tables 7-7, 7-8, 7-9, 7-10, 7-11, 7-12, 7-13, 7-14, and 7-15: Tables updated for clarification of windows and sample requirements.
35. Section 7.2.3.1: Section updated for clarification.
36. Section 7.2.4: Section updated for clarification.
37. Table 7-16: Table updated for clarification of windows and sample requirements.
38. Section 7.2.6: Section updated to add PRO details.
39. Section 8.2.2: Section updated to address FDA requirements for CRS and deaths.
40. Section 8.4: Section updates to address FDA requirements for follow-up after live birth
41. Section 10.5.4: Section updated for clarification.
42. Section 10.6.1: Section updated for clarification.
43. Section 10.6.1.3: Section updated for clarification.
44. Section 10.6.4: Section added for patient reported outcomes
45. Section 10.6.5: Section added for healthcare resource utilization
46. Section 13: New references added.

[redacted]

47. Section 14.1.2.3.5: Revision to ALL response guidelines

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/EC approval prior to implementation. In addition, if 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 amended protocol.

[redacted]

Protocol summary

Protocol number	CCTL019B2202
Title	A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia
Brief title	Study of efficacy and safety of CTL019 in pediatric ALL patients
Sponsor and Clinical Phase	Novartis Phase II Multicenter
Investigation type	Biological
Study type	Interventional
Purpose and rationale	Outcome remains poor for patients with relapsed or refractory (r/r) pediatric B-cell lineage acute lymphoblastic leukemia (B-cell ALL). Treatment options for r/r B-cell ALL include further treatment with salvage chemotherapy, second allogeneic stem cell transplantation (SCT) or supportive care. Therapy in this population is not curative with an overall survival of 3 to 6 months. CD19 has emerged as an attractive therapeutic target because 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 development of chimeric antigen receptor (CAR) T cells to target CD19+ cells (CART19 or CTL019) provides an innovative new approach to these malignancies. 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 in a Major Histocompatibility Complex (MHC) independent manner. Encouraging anti-tumor efficacy has been seen in r/r adult and pediatric ALL and in r/r CLL. Amendment 6 (US only): In patients up to 25 years with refractory or in second or greater relapse, CTL019 has shown the potential to be a definitive therapy, providing early, deep and durable remissions. Given the unprecedented responses in these difficult to treat patients, it has been hypothesized that CTL019 could be effective also in earlier lines of therapy in very high risk ALL patients, who have a poor prognosis and relapsed after first allo-HSCT, with a median survival of 7.4 months (95% Confidence Interval (CI), 6.0-9.6 months) (Crotta et al 2018). At Amendment 6 (US only), three cohort definitions are introduced (enrollment into Cohort 1 and Cohort 2 has been terminated as of 15-Jun-2020): • Main Cohort: all patients screened before protocol amendment 6 (enrollment into Main Cohort was completed at the time of the protocol amendment 6 release) • Cohort 1: patients who are very high risk at first relapse • Cohort 2: patients who received CTL019 within 6 months post allo-HSCT
Primary Objective(s)	For Main Cohort and Cohort 1 (enrollment into Cohort 1 has been terminated as of 15-Jun-2020): To evaluate the efficacy of CTL019 therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes Complete Remission (CR) and CR with incomplete blood count recovery (CRi) as determined by independent review committee (IRC) assessment. Cohort 2: To evaluate the feasibility and safety of CTL019 therapy in patients that relapsed < 6 months post allo-HSCT (enrollment into Cohort 2 has been terminated as of 15-Jun-2020)
Key Secondary Objectives	Key Secondary Objectives are only applicable for Main Cohort. Objective 1: Evaluate the efficacy of CTL019 therapy from US manufacturing facility as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment Objective 2: Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from all manufacturing facilities

[redacted]

	Objective 3: Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from US manufacturing facility
Secondary Objectives	Objective 1: To evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment. Objective 2: To evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment. Objective 3: To evaluate the duration of remission (DOR). Objective 4: To evaluate the relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS). Objective 5: Evaluate the response at Day 28 +/- 4 days Objective 6: Evaluate the impact of baseline tumor burden on response Objective 7: Evaluate the quality of response using MRD disease assessments before treatment and at day 28 +/- 4 days after treatment using central assessment by flow cytometry and before SCT by local assessment (flow or Polymerase Chain Reaction (PCR)). Objective 8: To evaluate the safety of CTL019 therapy as measured by type, frequency and severity of adverse events and laboratory abnormalities. Objective 9: To characterize the *in vivo* cellular pharmacokinetic (PK) profile (levels, persistence, trafficking) of CTL019 cells in target tissues (blood, bone marrow, Cerebral Spinal Fluid (CSF), and other tissues if available). Objective 10: To describe the prevalence and incidence of immunogenicity to CTL019. Objective 11: Describe the effect of CTL019 therapy on Patient Reported Outcome (PRO) Objective 12: To derive a score to predict cytokine release syndrome. Objective 13: To describe the profile of soluble immune factors that may be key to cytokine release syndrome. Objective 14: To describe the levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion for safety monitoring. Objective 15: To assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CTL019 manufactured by Fraunhofer Institute With Amendment 6 (US only), all above objectives remain unchanged and applicable for Main Cohort and for Cohort 1 and Cohort 2 except objective 15 (the following objective is no longer applicable; To assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CRL019 manufacture by Fraunhofer Institute). Enrollment into Cohort 1 and Cohort 2 has been terminated as of 15-Jun-2020.
Study design	This is a single arm, open-label, multi-center, phase II study to determine the efficacy and safety of CTL019 in pediatric patients with r/r B-cell ALL. The study will have the following sequential phases: Screening, Pre-Treatment (Cell Product Preparation & Lymphodepleting Chemotherapy), Treatment and Primary Follow-up, Secondary Follow-up (if applicable), and Survival Follow-up. The total duration of the study is 5 years from CTL019 cell infusion. After CTL019 infusion, efficacy will be assessed monthly for the first 6 months, then quarterly up to 2 years and semi-annually afterwards up to 5 years, or until patient relapse in the Treatment and Primary Follow-up phase. Safety will be assessed throughout the study. A post-study long term follow-up for lentiviral vector safety will continue under a separate destination protocol per health authority guidelines. At the beginning of the trial, a safety run-in stage will be conducted to enroll three patients for the purpose of assessing the acute safety profile of the Novartis designee manufactured CTL019 cell product. For the first three patients enrolled, following lymphodepleting chemotherapy and CTL019 infusion, safety profiles from the first 14 days post-infusion will be reported to the Health Authorities.
Population	At the time of protocol amendment 6, enrollment into the Main Cohort, including Japanese patients, has been completed. Main Cohort: The target population comprised of pediatric patients with B-cell ALL who were chemo-refractory, relapsed after allogeneic SCT, or were otherwise ineligible for allogeneic SCT. 97 patients were enrolled between the age of 3 years at the time of screening to the age of 27 years at the time of initial diagnosis. This included 65 infused patients less than the age of 18 at

<table>
<tr><td></td><td>the time of screening, 32 of which were under the age of 10. Patients 18 years of age or older at screening were limited to 10 total infused patients. When 10 patients ≥ 18 years of age have been infused, further enrollment in this age category required Sponsor approvalA total of 14 patients ≥ 18 years of age were infused after approval from Sponsor. 12 patients were enrolled to ensure at least 10 patients were infused with CTL019 manufactured by the Fraunhofer Institut für Zelltherapie und Immunologie, Leipzig, Germany (Fraunhofer-Institute), a contract manufacturing organization (CMO). 5 Japanese patients were screened to allow at least 3 additional patients to be infused with CTL019 manufactured by the US facility (total 5 Japanese patients infused). Sponsor approval was required to screen more than 5 patients, which was based on target number of infused patients.
For amendment 6 (US only), two additional cohorts (Cohort 1 and Cohort 2) were added to the study for the US participating sites. The target population (Cohort 1) comprised either patients with very high risk cytogenetic features at diagnosis - extreme hypodiploidy or t(17;19) with defined TCF3-HLF fusion – at the time of first relapse or any patient with B-cell ALL that relapses ≤ 36 months of initial diagnosis and who has MRD ≥0.01% at end of reinduction therapy.
Additionally, to investigate the feasibility and safety of administering CTL019 in patients with early relapse post allo-HSCT patients that relapsed less than 6 months post allo-HSCT, regardless of the number of relapses were also eligible (Cohort 2).
Approximately 20 patients were to be screened to ensure 15 infused patients (at least 10 in Cohort 1 and 5 in Cohort 2). 1 patient was enrolled into Cohort 1 and no patients were enrolled into Cohort 2. Enrollment into Cohort 1 and Cohort 2 has been terminated as of 15-Jun-2020).</td></tr>
<tr><td>Inclusion criteria</td><td>1. [Retired from Amendment Protocol Version 06]
2. For relapsed patients, documentation of CD19 tumor expression in bone marrow or peripheral blood by flow cytometry within 3 months of study entry
3. Adequate organ function defined as:
• Renal function defined as:
• A serum creatinine based on age/gender as follows:
<table>
<tr><td></td><td colspan="2">Maximum Serum Creatinine (mg/dL)</td></tr>
<tr><td>Age</td><td>Male</td><td>Female</td></tr>
<tr><td>1 to < 2 years</td><td>0.6</td><td>0.6</td></tr>
<tr><td>2 to < 6 years</td><td>0.8</td><td>0.8</td></tr>
<tr><td>6 to < 10 years</td><td>1.0</td><td>1.0</td></tr>
<tr><td>10 to < 13 years</td><td>1.2</td><td>1.2</td></tr>
<tr><td>13 to < 16 years</td><td>1.5</td><td>1.4</td></tr>
<tr><td>≥ 16 years</td><td>1.7</td><td>1.4</td></tr>
</table>
• Alanine Aminotransferase (ALT) ≤ 5 times the upper limit of normal (ULN) for age
• Bilirubin < 2.0 mg/dL
• Must have a minimum level of pulmonary reserve defined as ≤Grade 1 dyspnea and pulse oxygenation > 91% on room air
• Left Ventricular Shortening Fraction (LVSF) ≥ 28% confirmed by echocardiogram (ECHO), or Left Ventricular Ejection Fraction (LVEF) ≥ 45% confirmed by echocardiogram or Multiple Uptake Gated Acquisition (MUGA) within 7 days of screening
4. Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening
5. Life expectancy > 12 weeks
6. [Retired from Amendment Protocol Version 06]
7. Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50 at screening</td></tr>
</table>

	8. Signed written informed consent and assent forms if applicable must be obtained prior to any study procedures 9. Must meet the institutional criteria to undergo leukapheresis or have an acceptable, stored leukapheresis product 10. Once all other eligibility criteria are confirmed, must have a leukapheresis product of non-mobilized cells received and accepted by the manufacturing site. Note: Leukapheresis product will not be shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria is received. 11. (Protocol Amendment 6 US only) B-cell acute lymphoblastic leukemia and; Cohort 1: a. First relapse AND hypodiploid cytogenetics: fewer than 44 chromosomes and/or DNA index < 0.81, or other clear evidence of a hypodiploid clone OR b. First relapse AND t(17;19) with defined TCF3-HLF fusion OR c. First relapse with any cytogenetics provided the relapse occurred ≤ 36 months of initial diagnosis AND MRD at end of reinduction therapy is ≥0.01% by flow cytometry (local assessment) Cohort 2: a. Any BM relapse after allogeneic stem cell transplantation (HSCT) and must be < 6 months from HSCT at the time of CTL019 infusion 12. (Protocol Amendment 6 US only) Age up to 25 years at the time of screening
Exclusion criteria	1. Isolated extra-medullary disease relapse 2. Patients with concomitant genetic syndromes associated with bone marrow failure states: such as patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome. Patients with Down Syndrome will not be excluded. 3. Patients with Burkitt's lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell [surface Immunoglobulin (sIg) positive and kappa or lambda restricted positivity] ALL, with French-American-British [FAB] L3 morphology and /or a MYC translocation) 4. Prior malignancy, except carcinoma *in situ* of the skin or cervix treated with curative intent and with no evidence of active disease 5. Treatment with any prior gene therapy product 6. Has had treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy 7. Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening 8. Human Immunodeficiency Virus (HIV) positive test within 8 weeks of screening 9. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD) 10. [Retired from Amended Protocol Version 01] 11. Active Central Nervous System (CNS) involvement by malignancy, defined as CNS-3 per National Comprehensive Cancer Network (NCCN) guidelines. Note: Patients with history of CNS disease that has been effectively treated will be eligible 12. Patient has received an investigational medicinal product within the last 30 days prior to screening 13. [Retired from Amendment Protocol Version 06] 14. [Retired from Amended Protocol Version 02] 15. [Retired from Amended Protocol Version 02] 16. [Retired from Amended Protocol Version 04] 17. The following medications are excluded: a. **Steroids:** Therapeutic systemic 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

[redacted]

	b. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion c. **GVHD therapies:** Any systemic drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-tumor necrosis factor [anti-TNF], anti-interleukin 6 [anti-IL6] or anti-interleukin 6 receptor [anti-IL6R], systemic steroids) d. **Chemotherapy:** • Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion • The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate <25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated) • The following drugs must be stopped > 2 weeks prior to CTL019 infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside > 100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs • Pegylated-asparaginase must be stopped > 4 weeks prior to CTL019 infusion e. **CNS disease prophylaxis:** • CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate) f. Radiotherapy • Non-CNS site of radiation must be completed > 2 weeks prior to CTL019 infusion • CNS directed radiation must be completed > 8 weeks prior to CTL019 infusion g. **Anti T-cell Antibodies:** Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to CTL019 is prohibited since residual lytic levels may destroy the infused CTL019 cells and/or prevent their in vivo expansion. If such an agent has been administered within 8 weeks prior to CTL019, contact the Sponsor, consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion. 18. [Retired from Amendment Protocol Version 06] 19. Pregnant or nursing (lactating) women. NOTE: Female study participants of reproductive potential must have a negative serum pregnancy test performed within 24 hours before leukapheresis, lymphodepletion and prior to CTL019 infusion. 20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they agree to use highly effective methods of contraception from signing informed consent and through at least 12 months after the CTL019 infusion and until CAR T-cells are no longer present by Quantitative Polymerase Chain Reaction (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 (have had 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

[redacted]

	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. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. NOTE: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF). 21. Sexually active males must use a condom during intercourse from signing informed consent to at least 12 months after the 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. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.
Investigational and reference therapy	Main Cohort: A target per-protocol dose of CTL019 transduced cells will consist of a single infusion of 2.0 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 1.0 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). The following cell dose ranges may be infused if all other safety release criteria are met: 0.2 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg) **Amendment 6 only:** Cohort 1 and Cohort 2 (US only): Based on the patients' weight at the time of leukapheresis: • Patients ≤ 50 kg: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight • Patients > 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells
Efficacy assessments	**Primary:** ORR, which includes CR and CRi, as determined by assessments of peripheral blood, bone marrow, CNS symptoms, physical exam (PE) and CSF. The primary endpoint will be based on the IRC assessment. The local investigator's assessed results will be used for sensitivity analysis. **Secondary:** Patients with CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment, patients who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment, Minimal residual disease, duration of remission, relapse-free survival, event-free survival, and overall survival
Safety assessments	Adverse events and laboratory abnormalities (type, frequency and severity) Immunogenicity assessments : a. prevalence of immunogenicity against CTL019 (pre-existing), both humoral and cellular b. incidence of immunogenicity against CTL019, both humoral and cellular c. proportion of patients with transient anti-CTL019 antibody assay titers

[redacted]

	d. proportion of patients with sustained anti-CTL019 antibody assay titers
Other assessments	Pharmacokinetic assessments planned for this trial include: • Detection of CTL019 in blood, bone marrow and CSF (if available) by Quantitative Polymerase Chain Reaction (q-PCR). • Expression of CTL019 detected by flow cytometry in blood and bone marrow • Maximum Concentration (Cmax), Time of Peak Concentration (Tmax), Area Under the Curve (AUCs) and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF (if available). • Maximum extent of expansion of CTL019 in blood • Persistence of CTL019 in blood, bone marrow and CSF Exploratory objectives and biomarker assessments planned for this trial include: • [redacted] • T cell trafficking (CTL019 immunophenotyping) • Quantify the relationship between 1) CTL019 cell product/leukapheresis product [redacted] 2) other cell product/leukapheresis product characteristics and clinical endpoints (efficacy, safety, PK) • Describe the effect of anti-cytokine therapy on Cytokine Release Syndrome (CRS), CTL019 Pharmacokinetics/Pharmacodynamics (PK/PD), and tumor response • Explore the relationship between CRS, initial tumor burden, clinical tumor response, and PK/PD parameters • [redacted] • To describe hospital resource utilization
Data analysis	**Main Cohort:** **Primary endpoints:** An interim analysis will be performed when the first 50 patients who receive CTL019 have completed 3 months from study day 1 infusion or discontinued earlier. The final analysis of the primary endpoint will be performed after all patients infused with CTL019 and have completed 3 months follow-up from study day 1 infusion or discontinued earlier. Selected efficacy and safety analyses will be updated annually. A final Clinical Study Report (CSR) will be produced once all patients complete the study. The primary efficacy endpoint, ORR will be analyzed based on the data observed by IRC in the interim efficacy analysis set (IEAS) or the full analysis set (FAS) at time of interim and final analysis respectively. The primary efficacy analysis will be performed by testing the null hypothesis of the ORR being less than or equal to 20% against the alternative hypothesis the ORR is greater than 20% at overall one-sided 2.5% level of significance. The ORR will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets. The study will be considered successful if the lower bound of the 2-sided 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. Sensitivity analyses will be performed on the Enrolled Set, the per-protocol set (PPS) and with all patients who satisfy all clinical eligibility criteria (defined as all inclusion/exclusion criteria except that which pertains to the leukapheresis product) using the same method as described above. Additional sensitivity analysis will be performed using the ORR as assessed by local investigators. **Secondary endpoints:** Key secondary endpoints include ORR in all patients who received CTL019 from US manufacturing facility, and the rate of remission with MRD negative bone marrow in patients who received CTL019 from all manufacturing facilities and separately in patients who received CTL019 from US manufacturing facility. Hypotheses testing of key secondary endpoints will follow a hierarchical testing scheme so that the family-wise type I error rate will be controlled at one-sided 2.5% level.

[redacted]

	Analysis of other secondary or exploratory endpoints will be descriptive and may include summary statistics such as means, standard deviations, 95% confidence intervals, if applicable. Cumulative Incidence Functions (CIF), Kaplan-Meier curves and median time to event will be presented for time-to-event variables (DOR, RFS, EFS and OS), if appropriate. **Sample size:** In a previous study of clofarabine in pediatric patients with r/r B-cell ALL who have had 2 or more prior regimens, the reported ORR was 20%. Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR >20%, up to 76 patients in the FAS will provide more than 95% power to demonstrate statistical significance at one-sided 2.5% level of significance, if the underlying ORR is 45%. Accounting for the patients to assess CTL019 manufactured from the Fraunhofer Institute, and assuming 20% to 25% enrolled patients will not be infused due to reasons such as CTL019 product manufacturing issues, worsening of patient's condition, etc., approximately 95 patients need to be enrolled. **Cohort 1 and Cohort 2 (US only):** Patients in Cohort 1 and Cohort 2 will be analyzed separately. At the time of enrollment termination, only 1 patient was enrolled and infused in Cohort 1. Therefore, only listings will be presented for this single patient.
Key words	Relapsed/refractory ALL, relapsed ALL post allogeneic SCT, CTL019

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

B cell malignancies comprise a heterogeneous group of neoplasms including acute lymphoblastic leukemias (ALL), chronic lymphocytic leukemias (CLL), and a vast majority of non-Hodgkin's lymphomas (NHL). An estimated 91,000 new cases of lymphocytic leukemia and NHL were diagnosed in the US in 2012 (National Cancer Institute 2013). There were 66,371 lymphoid malignancies registered in 2000-2002 by 44 European cancer registries (Sant et al 2010). The majority of these malignancies are of B cell origin (Mitchell et al 2012).

ALL is more commonly seen in children although can occur at any age. ALL represent 75% to 80% of acute leukemias among children, therefore, making it the most common form of childhood leukemia (The Leukemia & Lymphoma Society 2009). The median age at diagnosis for ALL is 13 years; 60% of patients are diagnosed at younger than 20 years of age, whereas 23% are diagnosed at 45 years or older. Among children, B-cell lineage ALL constitutes approximately 88% of leukemia cases.

Current treatment for B cell malignancies include combinations of chemotherapy, radiation therapy, bone marrow transplantation, or peripheral blood and cord blood stem cell transplantation (SCT). Despite these treatment modalities, many relapsed patients remain incurable. Initial chemotherapy is typically administered over a 2 to 3 year period. With current multi-agent treatment regimens, the cure rate among children with ALL is > 80%. Most patients (>85%) with relapsed ALL will achieve a second remission (Ko et al 2010); however, the challenge remains to maintain remission. Most children who relapse once will relapse again, and will ultimately succumb to their disease. Leukemia is still the leading cause of death in pediatric oncology (Tallen et al 2010). Refractory ALL [never achieving a complete remission (CR)] in adults or children has a dismal prognosis and these patients do not benefit from SCT. Thus relapsed or refractory (r/r) ALL patients, both adult and pediatric, have significant unmet medical needs.

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 leukemias, 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 1989).

Adoptive T-cell therapy is one particular approach that involves engineering T-cell receptors (TCRs) to bind to specific antigens present on tumor cells. These modified TCRs, known as chimeric antigen receptors (CARs), allow the immune system to specifically target and destroy tumor cells in a MHC independent manner (Mellman et al 2011).

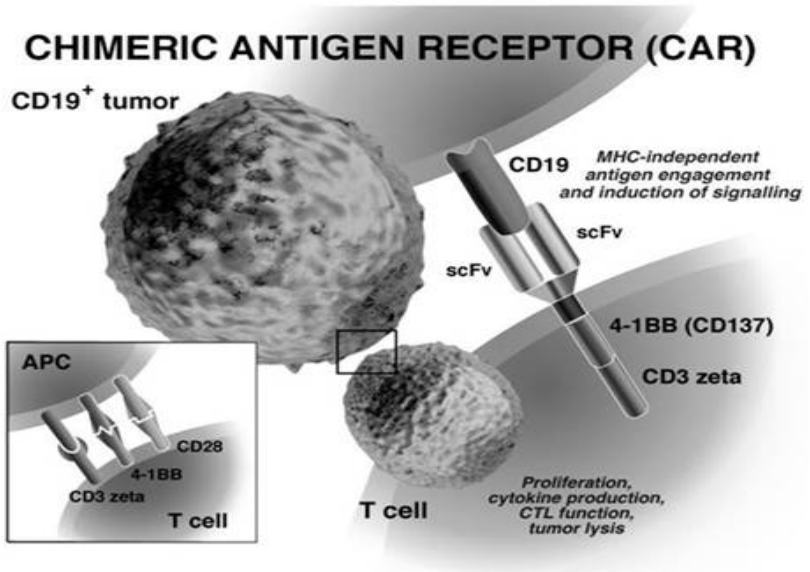
[redacted]

A very promising potential target antigen for B cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors (Sadelain 2003, Brentjens 2010, Porter 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 1988, Stamenkovic 1988, Fearon 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 1988, Stamenkovic 1988, Tedder 1989, Fearon 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, 4-1BBplus TCRζ (June 2007, June 2009, Kohn 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 transduced 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 1989, Pinthus 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) chains 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 2011, Grupp 2013, Maude 2014). It is anticipated that CTL019 may offer a therapeutic alternative for patients with r/r B cell

[redacted]

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 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.

1.2.1.1 Non-clinical experience

Extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models (Calogero 2000, Clay 2002, Hombach 2002, Pule 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 2000, Roessig 2002, Brentjens 2003, Cooper 2003, Serrano 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 1998, Krause 1998, Eshhar 2001, Maher 2002, Finney 2004, Friedmann-Morvinski 2005, Brentjens 2010). The pre-clinical data supporting CAR T cell persistence, expansion and anti-tumor efficacy have been published (Gross 1992, Milone 2009).

1.2.1.2 Clinical experience

For a summary of ongoing human studies with CTL019 (patients treated, disease indication, CTL019 dosing), please refer to the most current Investigator Brochure.Initial dosing in adults and children, for safety reasons, used a split infusion schedule of escalating doses. However, the majority of patients in the two phase I studies received CTL019 as a single one time infusion or two sequential infusions due to the onset of fevers and other clinical events precluding further infusions. For pediatric patients, cells are dosed per kg body weight where dosing in adults does not consider body weight.

Clinical efficacy

CTL019 has been approved by the FDA for the treatment of patients up to 25 years with B-cell precursor ALL that is refractory or in second or later relapse and of adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma [US Prescribing Information (PI) 2018]. European Medicines Agency (EMA) has approved CTL019 for the treatment of paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse, and of adult patients with r/r DLBCL after two or more lines of systemic therapy [European Union summary of product characteristics (EU SmPC) 2018]

Efficacy in r/r pediatric and young adult ALL

Treatment options for patients with r/r ALL include high-dose chemotherapy with subsequent HSCT, standard chemo-immunotherapy, targeted treatment with small molecule pathway inhibitors, or supportive care with non-curative palliative goals.

Three studies demonstrated the durable anti-tumor efficacy and safety of CTL019 and the cellular kinetics of CTL019 in pediatric and young adult patients with r/r B-ALL.

[redacted]

[CCTL019B2202] (B2202 global pivotal trial) and [CCTL019B2205J] (B2205J US trial) are very similar phase II, single arm, multicenter trials to determine the efficacy and safety of CTL019 in pediatric and young adult patients with r/r B-ALL. [CCTL019B2101J] (B2101J US trial) is a phase I/IIa single center study of CTL019 in pediatric patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma.

Study [B2202] met its primary objective at the interim analysis (IA) performed on the first 50 patients infused with CTL019 with data cut-off of 17-Aug-2016. The overall remission rate (ORR) during three months per Independent Review Committee (IRC) assessment was 82.0% (98.9% CI: 64.5, 93.3; $p<0.0001$). At the IA 2 with data cut-off of 25- Apr-2017 on 75 patients infused, 61/75 (81.3%) achieved ORR (Maude NEJM 2018). In addition, study [B2205J] again met its primary objective at the second interim analysis (IA) performed on 42 of 58 patients infused with CTL019 who completed 6 months of follow-up or discontinued early at the data cut-off of 06-Oct-2017.

Results from these two studies are consistent with that observed in B2101J where ORR was 94.6% (95% CI: 85.1, 98.9). ORR was consistent across all patient subgroups.

In all three studies, responses occurred rapidly (usually within 28 days post-CTL019 infusion) and bone marrow MRD data confirmed the depth of remission with all patients with CR or complete remission with incomplete blood count recovery (CRi) having MRD negative bone marrow (81.3%, 95% CI: 70.7, 89.4; $p<0.0001$ in study B2202; 64.3%, 95% CI: 48.0, 78.4 in study B2205J; and 85.7%, 95% CI: 73.8, 93.6 in study B2101J).

The median duration of remission (DOR) was not reached in studies [B2202] and [B2205J] and the estimated probability of remission at Month 6 was 79.5% and 71.4%, respectively. In study [B2101J], DOR at Month 6 was 73.9%.

The median overall survival (OS) in studies [B2202] was 19.1 months and [B2205J] was 23.8 months. The estimated probability of survival at Month 6 was 90.3% and 79.3%, respectively.

In study [B2101J], OS at Month 6 was 85.7%. The estimated probability of survival at Month 12 was 76% in study [B2202] and 62.2% in study [B2205J].

Across all three trials in pediatric and young adult r/r B-ALL patients, robust and high response rates occurred across the entire range of CTL019 doses and in all patient subgroups. In addition, consistently high and durable remissions were observed across these three studies in the majority of patients without additional therapies.

Furthermore, two different quality of life (QoL) tools demonstrated improvement in patient reported outcomes at 3 and 6 months compared to baseline following CTL019 infusion in study [B2202] further supporting the clinical benefit.

Clinical Safety in r/r ALL

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

[redacted]

Eleven deaths were reported for patients who received CTL019, of which 2 deaths occurred within 30 days of infusion. Seven were disease-related, three were attributed to infections, and one to intracerebral hemorrhage [Kymriah™ FDA 2017].

Cellular kinetics

Following infusion of CTL019, CAR-positive T cells in peripheral blood were observed to undergo significant expansion and demonstrated measurable persistence in vivo in CR/CRi patients. In pooled data from studies [B2202] and [B2205J] the Cmax and area under the curve from day 0 to 28 days following infusion in the cellular kinetic profile (AUC_{28d}) as determined by qPCR were higher in CR/CRi patients relative to non-responder (NR) patients: 104% higher for AUC_{28d} and 73.5% for Cmax (Thudium Mueller et al Clinical Cancer Research 2018). The trend was also observed in other indications (adult ALL and adult CLL). In Study [B2202], the cellular kinetics measured in bone marrow displayed high levels of transgene at Day 28 in CR/CRi patients. The transgene levels declined over time and were measurable at Month 3 and Month 6 in responder patients; however, the transgene levels in bone marrow were not measurable in bone marrow of NR patients beyond Day 28. Trafficking of CTL019 cells has also been demonstrated into the cerebral spinal fluid (CSF) in this patient population (Thudium Mueller at al Blood 2017). .

In the combined data pool, tocilizumab (interleukin-6 (IL-6) receptor-inhibitor monoclonal antibody) was used for the management of moderate/severe (grade 3 and 4) CRS in approximately 42.7% of patients treated with CTL019. Patients who receive tocilizumab for CRS often have higher CTL019 exposures (AUC_{28d}, area under the curve from day 0 to 84 days following infusion in the cellular kinetic profile (AUC_{84d}), and Cmax) compared to patients who did not receive tocilizumab while CTL019 Tmax is comparable. The higher CTL019 exposures observed in patients treated with tocilizumab is associated with a greater severity of CRS, which in turn correlates with higher tumor burden just prior to CTL019 cell infusion. In addition, CTL019 cells continued to expand and persist, as measured by transgene levels following CTL019 infusion （Thudium Mueller et al Clinical Cancer Research 2018).

For further information refer to the [CTL019 Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

Outcome remains poor for patients with r/r pediatric B-cell lineage acute lymphoblastic leukemia (B-cell ALL). Treatment options for r/r B-cell ALL include further treatment with salvage chemotherapy, second allogeneic stem cell transplantation (SCT) or supportive care. Therapy in this population is not curative with an overall survival of 3 to 6 months (Smith 2010, Tallen 2010, Martin 2012, Ko 2010, Duval 2010, Oudot 2008). As an example, clofarabine was approved by the Food and Drug Administration (FDA) for the treatment of pediatric patients with r/r ALL after at least 2 prior therapeutic regiments. The overall remission rates were 30% for ALL and 38% for Acute Myeloid Leukemia (AML) in Phase I studies (Jeha et al 2004); 30% (20% CR or complete remission with incomplete platelet recovery [CR_p] and 10% Partial Remission [PR]) for ALL and 26% for AML in Phase II studies (Jeha et al 2006). The median

duration of remission for patients with ALL who achieved at least a partial remission was 9.7 weeks (range 7 to 335 days) in the Phase II study.

CD19 has emerged as an attractive therapeutic target because 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 development of CAR T cells to target CD19+ cells (CART19 or CTL019) provides an innovative new approach to these malignancies. This approach involves recipient-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 in an MHC independent manner. Encouraging anti-tumor efficacy has been seen in r/r adult and pediatric ALL and in r/r CLL.

Amendment 6 for US only (enrollment has been terminated as of 15-Jun-2020): In patients up to 25 years with refractory or in second or greater relapse, CTL019 has shown the potential to be a definitive therapy, providing early, deep and durable remissions. Given the unprecedented responses in these difficult to treat patients, it has been hypothesized that CTL019 could be effective also in earlier lines of therapy in very high risk ALL patients, who have a poor prognosis, with a median survival of 7.4 months (95% CI, 6.0-9.6 months) (Crotta at al, 2018).

Very high risk ALL account for approximately 8-10% of all B-ALL patients and remains a therapeutic challenge. Certain biologic and response factors designate patients to be very-high risk children in the very high risk group include those with extreme hypodiploidy (44 or fewer chromosomes), t(9;22) (Philadelphia chromosome) BCR/ABL1 rearrangement, t(4;11) KMT2A (MLL) rearrangement, iAMP21 (intrachromosomal amplification of chromosome 21) amplification, those over 13 years of age in the United States, and/or failure to achieve complete remission at the end of induction therapy (>5 percent lymphoblasts in day 28 bone marrow or the presence of MRD). In the past, this group of patients had overall a poor prognosis, but subsets of these patients can be successfully treated with aggressive chemotherapy, often in combination with hematopoietic stem cell transplant and / or targeted therapy (such as imatinib for Ph+ ALL) with the rate of event free survival at 5 years being 40% with standard chemotherapy regimens in this population (Pulsipher et al 2011).

Augmentation of therapy to include allogeneic stem cell transplantation in first complete remission has been shown to improve disease free survival for a subset of this patient population, but it is associated with higher treatment related morbidity. Several studies have reported that transplantation in first complete remission results in a 5-year disease-free survival of 55%-60% for patients with very-high risk ALL, including a comparative analysis of transplantation to chemotherapy alone which resulted in a 16% survival benefit at 5 years from transplant (Fagioli et al 2013, Balduzzi et al 2005, Satwani et al 2007). Despite improvements in survival with allogeneic stem cell transplant, children with very-high risk ALL still have a 24% risk of relapse at 10 years compared with a 15% risk observed in standard-risk ALL patients (Fagioli et al 2013, Malempati et al 2007). Furthermore, the use of allogeneic stem cell transplantation is less effective if patient remains MRD positive after intensive chemotherapy or if patient has certain biological features such as extreme hyplodiploidy. Minimal residual disease status in ALL has been shown to predict the risk of relapse, event free survival and overall survival (EFS and OS) when measured during and after induction therapy in both newly diagnosed and relapsed ALL (Borowitz 2015). For example, in a study assessing outcomes after re-induction chemotherapy

[redacted]

for relapsed pediatric patients, at 5 years, EFS was 15% ± 6% in MRD positive patients while EFS was 56% ± 10% in MRD negative patients (Raetz et al 2012).

Early relapse is one of the strongest predictor of survival (time of relapse from initial diagnosis) and patients who relapsed less than 18 months after diagnosis had poor outcome, with a 5-yr survival rate of approximately 15-21% (Nguyen 2008. Leukemia 2008; 22 (12):2142). Patients with very high risk features tend to relapse rapidly after intensive chemotherapy, including post allogeneic stem cell transplantation.

2.2 Rationale for the study design

This is a single arm, multi-center, phase II study to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell ALL. A single arm study design is supported by the absence of effective therapies in this setting, and high unmet medical needs. This study will enroll approximately 95 patients to allow at least 50 infused patients less than the age of 18 at the time of screening, at least 10 of which will be under the age of 10. Patients 18 years of age or older at screening will be limited to 10 total infused patients. When 10 patients ≥ 18 years of age have been infused, further enrollment in this age category will require Sponsor approval. Approximately 14 patients will be enrolled to ensure at least 10 patients are infused with CTL019 manufactured by the Fraunhofer Institute. Approximately, 5 additional Japanese patients will be screened to allow at least 3 additional patients infused with CTL019 manufactured from the US facility (total 5 Japanese patients infused). Sponsor approval will be required to screen more than 5 patients, based on target number of infused patients. After assessment of eligibility, patients qualifying for the study will be enrolled and start lymphodepleting chemotherapy 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. The current trial will utilize product manufactured by Novartis or designee. *In vitro* studies assessing the comparability of these two products will have been completed prior to initiation of this protocol. 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 (ORR = CR + CRi) as determined by Independent Review Committee (IRC) assessment, including CR and CRi. The choice of ORR as the primary endpoint is based on evidence that ORR: 1) Is a standard outcome measurement in ALL; and 2) the established correlation with long-term outcome (Cheson 2003, Appelbaum 2007, NCCN v13 2013).

At the Amendment 6 (US only), three cohort definitions are introduced:

Main Cohort: all patients screened before protocol Amendment 6 (enrollment into Main Cohort was completed at the time of the protocol amendment 6 release)

Cohort 1 (US only): patients who are very high risk at first relapse (enrollment has been terminated as of 15-Jun-2020)

Cohort 2 (US only): patients who received CTL019 within 6 months post allo-HSCT (enrollment has been terminated early as of 15-Jun-2020)

[redacted]

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 1999, Surh 2000). Host lymphodepletion may enhance the effectiveness of adoptively transferred T cells (Dummer et al 2002). Homeostatic T cell proliferation can lead to activation of certain immune cell subsets (King et al 2004), providing a clue to improved anti-tumor responses. T cells can undergo up to seven rounds of cell division after being deprived of contact with antigen presenting cells (Kaech 2001, van Stipdonk 2001). Lymphodepletion eliminates regulatory T-cells and other competing elements of the immune system that act as "cytokine sinks", enhancing the availability of cytokines such as IL-7 and IL-15 (Klebanoff et al 2005). 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. Patients with myeloma have been treated with CARs and lymphopenia after lymphodepleting chemotherapy, and observed improved engraftment (Laport 2003, Rapoport 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).

In ongoing CTL019 pediatric ALL studies, 13 out of the first 16 patients infused with CTL019 cells received a lymphodepleting conditioning regimen prior to adoptive transfer of T cells. Six patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide and fludarabine, five patients received cyclophosphamide and etoposide, one patient received etoposide and cytarabine and one patient received cyclophosphamide alone. Of the three patients who did not receive a lymphodepleting conditioning regimen, two patients presented with Absolute Lymphocyte Count (ALC) < 1000 at the time of infusion.

2.3 Rationale for dose and regimen selection

Animal studies support 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 phase I cell dosing was divided among three split infusions (10%, 30% and 60% of the total cell dose). Of the 26 pediatric ALL patients that had a complete remission, 13 patients received a single infusion due to the onset of fevers, yet CRs were observed with either 1 to 3 infusions.

In phase I CLL studies, patients have shown responses after a single infusion or multiple infusions. In the phase II CLL trial, the dose has been given as a single infusion of 1 to 5 x 10^7 or 1 to 5 x 10^8 CTL019 transduced cells to study dose optimization. This single infusion was clinically well tolerated. No significant differences have been seen in responses or toxicity between these two doses. In responding CLL patients with CR or lasting PR, the CTL019 transduced cell numbers infused have ranged from 1.4 x 10^7 to 1.1 x 10^9 cells.

[redacted]

From the data collected to date in patients with CLL and ALL, there does not appear to be a discernible dose-response relationship with CTL019 transduced cell numbers infused. This is likely the result of CTL019 transduced cells ability 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. Additional considerations in this dose selection take into account the manufacturing feasibility of producing adequate numbers of CTL019 transduced cells.

In pediatric ALL patients who were treated in the CHP959 study, patients received once, two or three CTL019 infusions. Tumor responses were seen with each of these dosing schedules. Nineteen patients within the CHP959 study received only a single infusion of CTL019 due to the onset of fever with a cell range of 1.1 x 10^6 to 6.3 x10^6 CTL019 cells per kg with an acceptable safety profile. At the lower end of this dose range there is concern that doses less than 2 x 10^6 cells/kg may be associated with a lack of response or CR with an early relapse however the data at lower doses is limited.

Several patients received total CTL019 cell dose of over 5 x 10^8 cells (e.g. 6.8, 7.8 and 9.1 x 10^8 total CTL019 cells). Since the experience with these higher doses is more limited, a cut off of 2.5 x 10^8 cells as a maximum dose, based upon a weight >50 kg, is proposed. Manufacturing consideration and practicality were also considered in the dosing selection.

Therefore, for patients in Main Cohort, the targeted per-protocol CTL019 cell dose range for pediatric ALL patients ≤ 50 kg is 2.0 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight. For patients > 50 kg, the target dose is 1.0 to 2.5 x 10^8 autologous CTL019 transduced viable T cells.

In the Protocol Amendment 6 (US only), the dosing for the Cohort 1 and Cohort 2 was determined as per the label information (enrollment has been terminated as of 15-Jun-2020)

Based on the patients' weight at the time of leukapheresis:

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

2.3.1 Allowable infused cell dose range of CTL019 product

The allowable cell dose ranges are as follows:

- Patients ≤ 50 kg: 0.2 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight
- Patients > 50 kg: 0.1 to 2.5 x 10^8 autologous CTL019 transduced viable T cells

Products falling below the minimum values in the above allowable cell dose ranges will not be released for infusion.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

[redacted]

2.6 Risks and benefits

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria, pre-infusion criteria, CRS treatment algorithm, study procedures, and close clinical monitoring. There may be unforeseen risks with CTL019 which could be serious or potentially life threatening. Refer to [Investigator Brochure] for further details.

No preclinical reproductive studies have been conducted with CTL019 to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether CTL019 has the potential to be transferred to the fetus via the placenta and could cause fetal toxicity (including B-cell lymphocytopenia), or transmission of CTL019 via seminal fluid may occur. WOCBP and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. No data are currently available to determine the duration of contraception after receiving CTL019. There is no information regarding the presence of CTL019 in human milk, the effect on the breast-fed child or the effects of CTL019 on milk production.

Based on the observed efficacy as assessed by high response rates and lasting remissions of CTL019 therapy in pediatric patients with r/r B cell ALL, the potential benefit of CTL019 therapy in the target patient population treated in study CCTL019B2202 outweighs the potential risks of the therapy. CRS is identified as a clinically significant risk of CTL019 treatment. To address this risk a CRS treatment algorithm and CRS grading scale has been specifically developed and utilized for CTL019. In addition, logistical measures are also recommended to further manage this safety risk: patients are required to stay near the treatment site for the first 21 days, patients are required to stay with a caregiver and record twice daily temperatures during first two weeks, and patients/caregivers are required to carry patient identification card with investigator contact information. Refer to Section 6.2.4.2 for details on CRS management.

3 Objectives and endpoints

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

Note that the hypotheses testing for key secondary objectives are applicable to main cohort only.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
Main Cohort and Cohort 1* Evaluate the efficacy of CTL019 therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment	ORR (= CR + CRi) assessment; See Appendix 1 for response definition	Refer to Section 10.4.
Cohort 2*: To evaluate the feasibility and safety of CTL019 therapy in patients that relapsed < 6 months post allo-HSCT	Type, frequency and severity of adverse events and laboratory abnormalities	
Key secondary (For Main Cohort only)		
Evaluate the efficacy of CTL019 therapy from US manufacturing facility as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment	ORR (= CR + CRi) assessment; See Appendix 1 for response definition	Refer to Section 10.5.1.1
Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from all manufacturing facilities	Percentage of patients with BOR of CR or CRi with MRD negative bone marrow by flow cytometry during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from all manufacturing facilities	Refer to Section 10.5.1.2
Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from US manufacturing facility	Percentage of patients with BOR of CR or CRi with MRD negative bone marrow by flow cytometry during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from US manufacturing facility	Refer to Section 10.5.1.3.
Other secondary (For Main Cohort, Cohort 1* and Cohort 2*)		
Evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment	Percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment	Refer to Section 10.5.2.1

[redacted]

Objective	Endpoint	Analysis
Evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment	• Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment • In addition, all patients that proceed to SCT after CTL019 infusion will be described	Refer to Section 10.5.2.2.
Evaluate the duration of remission (DOR)	• DOR, i.e. the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to ALL • Site of involvement of subsequent relapse will be summarized	Refer to Section 10.5.2.3.
Evaluate the relapse-free survival (RFS)	RFS, i.e. the time from achievement of CR or CRi whichever occurs first to relapse or death due to any cause during CR or CRi	Refer to Section 10.5.2.4.
Evaluate the event-free survival (EFS)	EFS, i.e. the time from date of CTL019 infusion to the earliest of death, relapse or treatment failure	Refer to Section 10.5.2.5.
Evaluate the overall survival (OS)	OS, i.e. the time from date of CTL019 infusion to the date of death due to any reason	Refer to Section 10.5.2.6.
Evaluate the response at Day 28 +/- 4 days	Proportion of patients attaining CR or CRi at Day 28 +/- 4 days post CTL019 infusion	Refer to Section 10.5.2.8.
Evaluate the impact of baseline tumor burden on response	Response as a function of baseline tumor burden (tumor load) (MRD, extramedullary disease, etc.)	Refer to Section 10.5.2.9.
Evaluate the quality of response using MRD disease assessments before treatment and at day 28 +/- 4 days after treatment using central assessment by flow cytometry and before SCT by local assessment (flow or PCR)	MRD quantitative result (% leukemic cells) and qualitative result (positive/negative)	Refer to Section 10.5.2.10.
Evaluate the safety of CTL019 therapy	Type, frequency and severity of adverse events and laboratory abnormalities	Refer to Section 10.5.3.
Characterize the *in vivo* cellular pharmacokinetic (PK) profile (levels, persistence, trafficking) of CTL019 cells in target tissues (blood, bone marrow, CSF, and other tissues if available)	• CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available • Expression of CTL019 detected by flow cytometry in blood and bone marrow • Cmax, Tmax, AUCs and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF if available • Persistence of CTL019 in blood, bone marrow, and CSF if available (eg Mean Residence Time [MRT] last)	Refer to Section 10.5.4.

[redacted]

Objective	Endpoint	Analysis
Describe the prevalence and incidence of immunogenicity to CTL019	• Prevalence and incidence of immunogenicity and anti-CTL019 assay titers	Refer to Section 10.5.3.4.
Describe the effect of CTL019 therapy on Patient Reported Outcomes (PRO)	• PRO as measured by PedsQL and EQ-5D questionnaires	Refer to Section 10.5.2.7
Derivation of a score to predict cytokine release syndrome	• Develop a score utilizing clinical and biomarker data and assess its ability for early prediction of cytokine release syndrome	Refer to Section 10.5.3.5
Describe the profile of soluble immune factors that may be key to cytokine release syndrome	• Frequent monitoring of concentrations of soluble immune factors in blood	Refer to Section 10.5.3.6
Describe the levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion for safety monitoring	• Lymphocyte subsets of B and T cells and description of associated safety events	Refer to Section 10.5.3.7
Assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CTL019 manufactured by Fraunhofer Institute (this objective is no longer applicable for Cohort 1 and Cohort 2)	• ORR and MRD negative remission • Type, frequency and severity of adverse events and laboratory abnormalities • CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available	Refer to Section 10.5.2.11 Not applicable at Interim analysis
Exploratory (For Main Cohort, Cohort 1* and Cohort 2*)		
[redacted]	• [redacted]	Refer to Section 10.6.
T cell trafficking (CTL019 immunophenotyping)	• CTL019 positive T cells and other leukocyte subsets	Refer to Section 10.6.
Describe the effect of anti-cytokine therapy on CRS, CTL019 PK/PD, and tumor response	• Clinical CRS adverse events and laboratory measures of CRS (e.g. IL-6, C-reactive protein (CRP) and ferritin concentrations) by anti-cytokine therapy • CTL019 concentrations by anti-cytokine therapy • Disease response by anti-cytokine therapy	Refer to Section 10.6.

[redacted]

Objective	Endpoint	Analysis
Quantify the relationship between 1) CTL019 cell product/leukapheresis product [redacted] 2) other cell product/leukapheresis product characteristics and clinical endpoints (efficacy, safety, PK)	• [redacted] • Leukapheresis and cell product characteristics [redacted] • Clinical response (CR, CRi, relapse) • MRD and B cell recovery assay results • PK parameters • CRS status • Cytokine response	Refer to Section 10.6.

To explore the relationships between CRS, initial tumor burden, clinical tumor response, and PK/PD parameters	• CRS occurrence, CRS grade, need for anti-cytokine therapies
	  • Baseline tumor burden
	  • Clinical tumor response at Day 28
	  • CTL019 concentrations and B cell depletion
		Refer to Section 10.6.

[redacted]	[redacted]	Refer to Section 10.6.
To describe hospital resource utilization	• Number of patients with hospitalized infusion, total number of hospitalizations, and length of stay	Refer to Section 10.6.

*Enrollment into Cohort 1 and Cohort 2 has been terminated of 15-Jun-2020. Endpoints will only be presented as listings for the single patient in Cohort 1.

[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 pediatric patients with relapsed or refractory B-cell ALL (Main Cohort). Enrollment into the Main Cohort was completed at the time of protocol amendment 6). For Amendment 6 (US only), the efficacy and safety of patients that are very high risk at first relapse (Cohort 1) OR that received CTL019 within 6 months post allo-HSCT will be studied (Cohort 2). Enrollment in US only Cohorts 1 and 2 has been terminated early as of 15-Jun-2020) The study will have the following sequential phases for all patients: Screening (Section 7.1.1), Pre-Treatment (Cell Product Preparation and Lymphodepleting Chemotherapy; Section 7.1.2), Treatment and Primary Follow-up (Section 7.1.3), Secondary Follow-up (if applicable, Section 7.1.4), and Survival Follow-up (Section 7.1.5). The total duration of the study is 5 years. After CTL019 infusion, efficacy will be assessed monthly for the first 6 months, then quarterly up to 2 years and semi-annually afterwards up to 5 years, or until patient relapse. Efficacy assessments will be based on the Novartis guidelines for response assessment in ALL (Appendix 1), which is based on NCCN version 1.2013 guidelines, Cheson et al (2003) and Appelbaum et al (2007). Safety will be assessed throughout the study. A post-study long term follow-up (Section 7.1.6) for lentiviral vector safety will continue under a separate destination protocol per the following health authority guidelines: FDA (2006a), FDA (2006b), European Medicines Agency (EMA) (2008) and EMA (2009).

At the beginning of the trial, a **safety run-in stage** will be conducted to enroll three patients for the purpose of assessing the acute safety profile of the Novartis CTL019 cell product. 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-cell ALL. This data demonstrates that the majority of tumor lysis syndrome (TLS), cytokine release syndrome and chemotherapy toxicities have manifested within the first two weeks post-CTL019 infusion in r/r ALL patients. The first three patients will be enrolled in a staggered manner (waiting 14 days prior to treating the next patient) for the purpose of assessing the acute and subacute safety profile. Safety profiles during the first 14 days post infusion will be reported to the Health Authorities.

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:

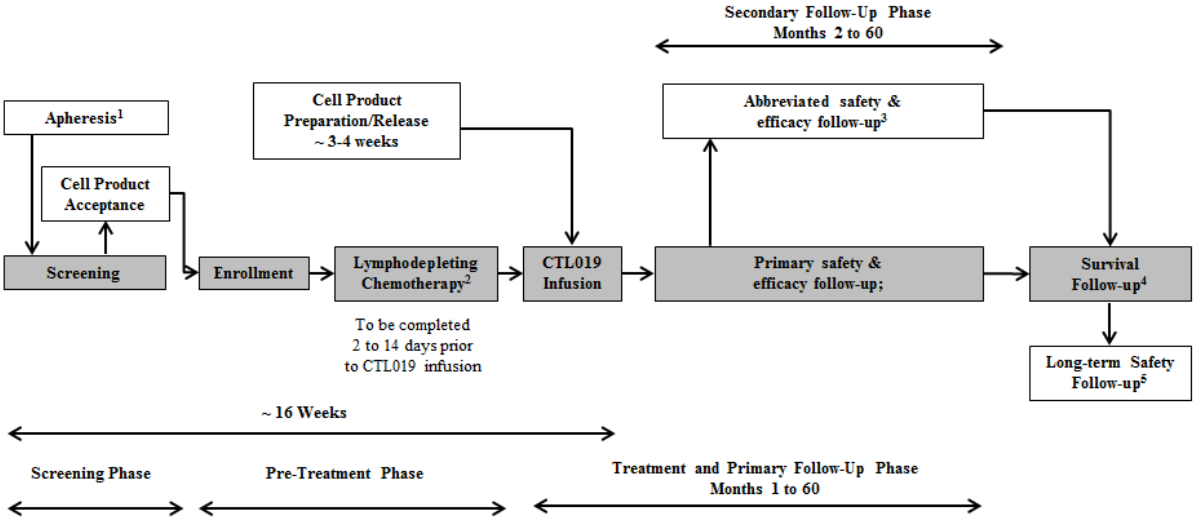
- 1st patient enrollment, wait 14 days
- 2nd patient enrollment, wait 14 days
- Following completion of this staggered enrollment of the first two patients, the new site may then proceed with enrollment of patients without the stagger.

[redacted]

Initially, manufacturing of CTL019 has been performed at the Novartis Morris Plains manufacturing facility and will be expanded to the Fraunhofer Institute to establish a CTL019 manufacturing site in Europe. Approximately 14 patients will be enrolled in Region Europe to allow at least 10 patients infused with CTL019 manufactured at the Fraunhofer Institute.

In order to support the development of CTL019 in Japan, at least 5 patients were to be infused. 2 patients from Japan have been infused with CTL019. At least 5 additional Japanese patients will be screened to allow at least 3 additional patients to be infused with CTL019 manufactured from the US facility (total 5 Japanese patients infused). Sponsor approval will be required to screen more than 5 patients, which based on target number of infused patients.

Figure 4-1 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

Cryopreserved 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 by the manufacturing facility. If a historical leukapheresis product is not available, leukapheresis will be performed after informed consent signature.

Following informed consent, information on the patients' leukapheresis material including sample sentinel vials collected from leukapheresis (when available) will be sent to Novartis manufacturing separately or together with leukapheresis product.

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

[redacted]

Patients in the Main cohort only may be consented for the Novartis leukapheresis protocol (CTL019B2206) prior to or after consent has been obtained for the CTL019 treatment protocol dependent upon local requirements.

For patients developing grade 2 to 4 acute GVHD or extensive chronic GVHD following the collection of a leukapheresis product, such a leukapheresis product cannot be used for CTL019 manufacturing or infusion due to concerns of auto-reactive T cells with an increased risk for inducing or exacerbating GVHD by the manufactured product.

During the screening phase, informed consent/assent will be signed and all clinical eligibility criteria (defined as all inclusion/exclusion criteria except that which pertains to the leukapheresis product) will be assessed. Only following informed consent/assent and confirmation of all clinical eligibility criteria will the patient's leukapheresis product and sentinel vial(s), as requested by the manufacturing facility, be shipped to the manufacturing facility. The manufacturing facility will then evaluate the patient's leukapheresis product for acceptance. Enrollment is defined as the point at which the patient meets all clinical inclusion/exclusion criteria, and the patients' leukapheresis product is received and accepted by the manufacturing facility.

[redacted]

4.2 Definition of end of the study

The end of study is defined as the last patient's last visit (LPLV) in Main Cohort, which is the last patient's Month 60 evaluation, or the time of premature withdrawal. The one patient in Cohort 1 will be rolled-over to the Long-Term Follow-Up protocol at the end of study upon consent.

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: 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 on all patients under a separate destination protocol as recommended by health authority guidance for patients treated with gene therapies. All patients who either complete the study or prematurely discontinue from the study will be enrolled in this destination protocol at the time of study completion/discontinuation (separate informed consent/assent forms will be provided for this protocol; Section 7.1.6).

Patients may continue to be followed under the current protocol for survival until end of study as defined above or until they choose to enroll into the long term follow-up protocol ([CCTL019A2205B]), whichever occurs first. The survival follow-ups can be conducted via the form of telephone contact.

[redacted]

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. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. For patients who have received a CTL019 infusion, a long term post-study follow-up for lentiviral vector safety will still continue under a separate destination protocol for 15 years post infusion per health authority guidelines. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the early termination of the trial.

5 Population

5.1 Patient population

At the time of protocol amendment 6, enrollment into the Main Cohort including Japanese patients, has been completed. The target in Main Cohort population consisted of pediatric patients with B-cell ALL who were chemo-refractory, relapsed after allogeneic SCT, or were otherwise ineligible for allogeneic SCT. 97 patients were enrolled between the age of 3 years at the time of screening to the age of 27 years at the time of initial diagnosis. This included 65 infused patients less than the age of 18 at the time of screening, 32 of which were under the age of 10. Patients 18 years of age or older at screening were limited to 10 total infused patients. When 10 patients ≥ 18 years of age have been infused, further enrollment in this age category required Sponsor approval. A total of 14 patients ≥ 18 years of age were infused after approval from Sponsor. 12 patients were enrolled to ensure at least 10 patients were infused with CTL019 manufactured by the Fraunhofer Institute. The investigator or designee ensured that only patients who met all the following inclusion and none of the exclusion criteria were offered treatment in the study.

[JAPAN ONLY: In order to support the development of CTL019 in Japan, at least 5 Japanese patients were to be infused with CTL019. 2 patients from Japan have been infused with CTL019. 5 additional Japanese patients were screened to allow at least 3 additional patients to be infused with CTL019 manufactured from the US facility (total 5 Japanese patients infused).] Sponsor approval was required to screen more than 5 patients, which was based on target number of infused patients.

For amendment 6 (US only), two additional cohorts (Cohort 1 and Cohort 2) were added to the study for the US participating sites in the previous main cohort. The target population for Cohort 1 comprised either patients with very high risk cytogenetic features at diagnosis - extreme hypodiploidy defined as fewer than 44 chromosomes and/or DNA index less than 0.81, or t(17;19) with defined TCF3-HLF fusion – at the time of first relapse or any patient with B-cell ALL that relapses ≤ 36 months of initial diagnosis and who has MRD ≥0.01% at end of reinduction therapy.

Additionally, to investigate the feasibility and safety of administering CTL019 in patients with early relapse post allo-HSCT patients that relapsed less than 6 months post allo-HSCT, regardless of the number of relapses were also eligible (Cohort 2). Approximately 20 patients

[redacted]

were to be screened to ensure 15 infused patients (at least 10 in Cohort 1 and 5 in Cohort 2). 1 patient was enrolled into Cohort 1 and no patients were enrolled into Cohort 2.

Enrollment into Cohorts 1 and 2 has been terminated as of 15-Jun-2020.

5.2 Inclusion criteria

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

1. [Retired from Protocol Amendment Version 06]
2. For relapsed patients, CD19 tumor expression demonstrated in bone marrow or peripheral blood by flow cytometry within 3 months of study entry
3. Adequate organ function defined as:
   a. Renal function defined as:
      - A serum creatinine based on age/gender as follows:

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

   b. ALT ≤ 5 times the ULN for age
   c. Bilirubin < 2.0 mg/dl
   d. Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation > 91% on room air
   e. LVSF ≥ 28% confirmed by echocardiogram, or LVEF ≥ 45% confirmed by echocardiogram or MUGA within 7 days of screening
4. Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening
5. Life expectancy > 12 weeks
6. [Retired from Protocol Amendment Version 06]
7. Karnofsky (age ≥16 years) or Lansky (age < 16 years) performance status ≥ 50 at screening
8. Signed written informed consent and assent forms if applicable must be obtained prior to any study procedures
9. Must meet the institutional criteria to undergo leukapheresis or have an acceptable, stored leukapheresis product
10. Once all other eligibility criteria are confirmed, must have a leukapheresis product of non-mobilized cells received and accepted by the manufacturing site. Note: Leukapheresis product will not be shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria is received
11. (Protocol Amendment 6 US only) B-cell acute lymphoblastic leukemia and:

[redacted]

Cohort 1:

a. First relapse AND hypodiploid cytogenetics: fewer than 44 chromosomes and/or DNA index < 0.81, or other clear evidence of a hypodiploid clone OR
b. First relapse AND t(17;19) with defined TCF3-HLF fusion OR
c. First relapse with any cytogenetics provided the relapse occurred ≤ 36 months of initial diagnosis AND MRD at end of reinduction therapy is ≥0.01% by flow cytometry (local assessment)

Cohort 2 (US only):

a. Any BM relapse after allogeneic stem cell transplantation (allo-HSCT) and must be < 6 months from HSCT at the time of CTL019 infusion

12. (Protocol Amendment 6 US only) Age up to 25 years at the time of screening

5.3 Exclusion criteria

Patients meeting any of the following criteria must be excluded from the study:

1. Isolated extra-medullary disease relapse
2. Patients with concomitant genetic syndromes associated with bone marrow failure states: such as patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome. Patients with Down Syndrome will not be excluded.
3. Patients with Burkitt's lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell [sIg positive and kappa or lambda restricted positivity] ALL, with FAB L3 morphology and /or a MYC translocation)
4. Prior malignancy, except carcinoma *in situ* of the skin or cervix treated with curative intent and with no evidence of active disease
5. Treatment with any prior gene therapy product
6. Has had treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
7. Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening
8. Human Immunodeficiency Virus (HIV) positive test within 8 weeks of screening
9. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD)
10. [Retired from Amended Protocol Version 01]
11. Active CNS involvement by malignancy, defined as CNS-3 per NCCN guidelines. Note: Patients with history of CNS disease that has been effectively treated will be eligible
12. Patient has an investigational medicinal product within the last 30 days prior to screening
13. [Retired from Amended Protocol Version 06]
14. [Retired from Amended Protocol Version 02]
15. [Retired from Amended Protocol Version 02]
16. [Retired from Amended Protocol Version 04]
17. The following medications are excluded:

[redacted]

a. **Steroids:** Therapeutic systemic 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. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
c. **GVHD therapies:** Any systemic drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-TNF, anti-IL6 or anti-IL6R, systemic steroids)
d. **Chemotherapy:**
   - Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion
   - The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated)
   - The following drugs must be stopped >2 weeks prior to CTL019 infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside > 100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs
   - Pegylated-asparaginase must be stopped > 4 weeks prior to CTL019 infusion
e. **CNS disease prophylaxis:** CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)
f. **Radiotherapy**
   - Non-CNS site of radiation must be completed > 2 weeks prior to CTL019 infusion
   - CNS directed radiation must be completed > 8 weeks prior to CTL019 infusion
g. **Anti T-cell Antibodies:** Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to CTL019 is prohibited since residual lytic levels may destroy the infused CTL019 cells and/or prevent their in vivo expansion. If such an agent has been administered within 8 weeks prior to CTL019, contact the Sponsor, consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.

18. [Retired from Amended Protocol Version 06]
19. Pregnant or nursing (lactating) women. NOTE: Female study participants of reproductive potential must have a negative serum pregnancy test performed within 24 hours before leukapheresis, lymphodepletion and prior to CTL019 infusion.
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they agree to use highly effective methods of contraception from signing informed consent and through at least 12 months after the 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:

[redacted]

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or 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.

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

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

21. Sexually active males must use a condom during intercourse from signing informed consent to at least 12 months after the 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. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.

6 Treatment

6.1 Study treatment

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

[redacted]

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 expand *ex vivo* for approximately 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.

Main Cohort:

A target per-protocol dose of CTL019 transduced cells for pediatric patients will consist of a single infusion of 2.0 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 1.0 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). The following cell dose ranges may be infused if all other safety release criteria are met: 0.2 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patient ≤ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg).

Amendment 6 only: Cohort 1 and Cohort 2:

Based on the patients' weight at the time of leukapheresis:

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

6.1.1 Dosing regimen

6.1.1.1 Lymphodepleting chemotherapy

It is anticipated that many patients will have been receiving chemotherapy for relapse 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 preinfusion, lymphodepleting chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden.

When given, lymphodepleting chemotherapy should be started before CTL019 infusion so that CTL019 cells will be given 2 to 14 days after completion of the lymphodepleting chemotherapy. The chemotherapy start date will vary based on the selected chemotherapy. The purpose of this chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of 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 lymphodepleting regimen is:

- Fludarabine (30 mg/m^2 intravenously [i.v.] daily for 4 doses) and cyclophosphamide (500 mg/m^2 i.v. daily for 2 doses starting with the first dose of fludarabine)

If there was previous Grade 4 hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then the following will be used:

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

[redacted]

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.

6.1.1.2 CTL019 infusion

The CTL019 cell product will be released to the study site approximately 3 to 4 weeks after manufacturing has commenced, provided all required safety and quality release criteria have been met.

Prior to CTL019 infusion: the following criteria must be met:

1. **Influenza Testing:** 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, he/she should complete a full course of oseltamivir phosphate or zanamivir as described in the label (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their full course of treatment **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 may need to be considered.
2. **Performance Status:** Patient should not experience a significant change in clinical or performance 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.
3. **Laboratory Abnormalities:** Patients experiencing laboratory abnormalities after enrollment, that in the opinion of the treating investigator or PI may impact subject safety or the subjects' ability to receive the CTL019 infusion, may have their infusion delayed until it is determined to be clinically appropriate to proceed with the CTL019 infusion.
4. **Leukemia Disease Status:** Prior to CTL019 infusion and following lymphodepleting (LD) chemotherapy, patients must not have accelerating disease, as this will put them at unacceptable risk for severe CRS. Patients should not receive CTL019 infusion if they exhibit significant progression of disease during or following LD chemotherapy as evidenced by
   - Significant and increasing circulating blasts
   - Significant increases in organomegaly
   - Clinical evidence of new CNS disease
5. **Chemotherapy Toxicity:** Patients experiencing toxicities from their preceding lymphodepleting chemotherapy will have their infusion schedule delayed until these toxicities have been resolved (to grade 1 or baseline). 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

[redacted]

b. **Cardiac:** New cardiac arrhythmia not controlled with medical management. Pre-infusion ECG also required (Table 7-1).
c. **Hypotension:** requiring vasopressor support

6. **Infection:** CTL019 infusion must be delayed if there is an uncontrolled active infection, as evidenced by positive blood cultures for bacteria, fungus, or PCR positivity for viral DNA within 72 hours of CTL019 cell infusion, or clinical or radiographic evidence of active infection. Following the treatment of a recent infection, significant improvement must be established either clinically and/or radiographically, prior to CTL019 infusion
7. **GVHD Status:** Patients should not be infused if they develop grade 2-4 acute or extensive chronic GVHD since the time of screening.
8. **Concomitant Medications:** If patients are taking any of the following medications, their infusion must be delayed until the medications have been stopped according to the following:
   a. **Steroids:** Therapeutic systemic 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. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
   c. **GVHD therapies:** Any systemic drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as rituximab, anti-TNF, anti-IL6 or anti-IL6R, systemic steroids)
   d. **Chemotherapy:**
      - Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion
      - The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated)
      - The following drugs must be stopped > 2 weeks prior to CTL019 infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside > 100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs
      - Pegylated-asparaginase must be stopped > 4 weeks prior to CTL019 infusion
   e. **CNS disease prophylaxis:**
      - CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)
   f. **Radiotherapy**
      - Non-CNS site of radiation must be completed > 2 weeks prior to CTL019 infusion
      - CNS directed radiation must be completed > 8 weeks prior to CTL019 infusion

[redacted]

g. **Anti T-cell Antibodies:** Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to CTL019 is prohibited since residual lytic levels may destroy the infused CTL019 cells and/or prevent their in vivo expansion. If such an agent has been administered within 8 weeks prior to CTL019, contact the Sponsor, consider consultation with a pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.

9. **Stem Cell Transplant:** Reconfirm that patient is ≥ 6 months from SCT at the time of CTL019 infusion (if applicable)
10. **Lymphodepleting Chemotherapy Timing:** If a 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.
11. **Cardiac Evaluations:** In the event that the time between screening cardiac ECHO/MUGA and CTL019 infusion exceeds 6 weeks, cardiac imaging must be repeated to confirm a LVSF ≥ 28 % by echocardiogram, or LVEF ≥ 45 % by echocardiogram or MUGA.
12. **Pregnancy:** Patient must undergo a pregnancy test (serum) within 24 hours prior to infusion (Table 7-1).

Additional safety procedures prior to administration: The risk of 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.

The site must confirm that two doses of tocilizumab are on site **prior to CTL019 infusion** and one dose of siltuximab must be accessible within 24 hours of infusion for administration in order to manage suspected toxicities.

[JAPAN ONLY: The site must confirm that three doses of tocilizumab are on site **prior to CTL019 infusion** in order to manage suspected toxicities.]

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 an 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.

Cell thawing and infusion of CTL019 product: A study physician MUST evaluate the patient just prior to infusion to ensure the patient meets CTL019 infusion criteria. Trained study staff will administer the CTL019 infusion using precautions for immunosuppressed patients. Protective isolation should follow institutional standards and policies. Emergency medical equipment should be available during the infusion in case the patient has a significant reaction to the infusion such as anaphylaxis or severe hypotension.

[redacted]

The CTL019 dose will be administered via a single intravenous infusion. Depending on the volume of the CTL019 product, it will be given either as an i.v. infusionthrough a latex free i.v. tubing WITHOUT a leukocyte filter (approximately 10 – 20 mL per minute adjusted as appropriate for smaller children and smaller volumes) or as an i.v. push via a syringe (for smaller volumes). It is recommended that the infusion/i.v. push be completed within 30 minutes of thawing the cryopreserved product in order to preserve maximum cell viability. Vital signs (temperature, respiration rate, pulse, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion and then approximately every 15 minutes for one hour and repeated at 2 hours. If vital signs are unsatisfactory and unstable, continue to monitor the patient until vital sign stabilization.

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

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. Patient or patient's caregiver should monitor the patient's temperature twice a day for the first 14 days. The patient or patient's caregiver should be instructed to call the investigator promptly with any signs of fever for possible hospitalization.

Supportive care: Local guidelines will be followed for the supportive care of immunosuppressed and chemotherapy treated 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 Treatment for cytokine release syndrome

Management of CRS following CTL019 administration must follow the CRS treatment algorithm which has been updated to Lee grading system (Table 6-2) and revised CRS management algorithm in Table 6-1. CTL019 administration may require tocilizumab (recommended label dose 8 mg/kg for patients weighing ≥ 30 kg and 12 mg/kg for patients weighing < 30 kg; IV infusion over 1 hour), 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. 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 must be accessible **within 24 hours of infusion**. All other medications (except for tocilizumab or siltuximab administration), including steroids

[redacted]

given to treat CRS, must be listed on the concomitant medication CRF. Tocilizumab or siltuximab should be reported on the "Dosage Administration Record - Tocilizumab" or "Dosage Administration Record - Siltuximab" eCRF, respectively.

[JAPAN ONLY: Management of CRS following CTL019 administration must follow the Japan CRS treatment algorithm in Figure 6-2. CTL019 administration may require tocilizumab (recommended label dose 8 mg/kg for patients weighing ≥ 30 kg and 12 mg/kg for patients weighing < 30 kg; IV infusion over 1 hour), and steroids, for the treatment of suspected CRS toxicities as described below in Section 6.2.4.2. The site must confirm that three doses of tocilizumab are on site and available for administration **prior to CTL019 infusion**. All other medications (except for tocilizumab administration), including steroids given to treat CRS, must be listed on the concomitant medication CRF. Tocilizumab should be reported on the "Dosage Administration Record - Tocilizumab"eCRF, respectively.]

6.1.4 Guidelines for continuation of treatment

Not applicable.

6.1.5 Treatment duration

A single dose of CTL019 transduced viable T cells will be given.

6.2 Dose escalation guidelines

Not applicable.

6.2.1 Starting dose rationale

Not applicable.

6.2.2 Provisional dose levels

Not applicable.

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

Not applicable.

6.2.3.1 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

There are no dose-limiting toxicities in this protocol; however criteria for stopping or pausing the trial are detailed below.

[redacted]

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 hematologic 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 at the site level.

Premature termination of the clinical trial may occur because of a regulatory authority decision, 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

Beyond the **safety run-in stage**, the overall study will be paused, and health authorities notified if:

- 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 Sponsor, DMC, or any 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

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:

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

[redacted]

- Death suspected to be related to CTL019 therapy

6.2.4.2 General toxicity management considerations

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.

Febrile reaction

In the event of febrile reaction, an evaluation for infection should be initiated, and patients managed appropriately with antibiotics, fluids and other supportive care as medically indicated and determined by the treating physician. Inpatient treatment is recommended initially. In the event that the patient develops sepsis or systemic bacteremia following CTL019 cell infusion, appropriate cultures and medical management should be initiated. If a contaminated CTL019 cell product is suspected, the product can be retested for sterility using archived samples that are stored at the manufacturing site. Consideration of a cytokine release syndrome (see below) should be given.

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

Data from CTL019 treated patients experiencing CRS show marked elevations in IL6 and IFN-g. The symptoms generally occur 1-14 days after cell infusion in patients with ALL 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. Five patients with Grade 4 CRS have been treated with siltuximab in CTL019B2202 at clinical sites outside of Japan. If the patient experiences ongoing CRS despite administration of repeated anti-cytokine directed therapies with tocilizumab, steroids and siltuximab, anti-T-cell therapies such as cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab may be considered and need to be captured in case report forms. Fatal outcomes associated with CRS have been observed in pediatric and adult ALL patients in the context of current significant clinical infections.

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 Table 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

[redacted]

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 Table 6-1 below. Serum cytokine and inflammatory marker levels should NOT be used for clinical management decisions of CRS.

Cases of transient left ventricular dysfunction, as assessed by cardiac ECHO, have been reported in some patients with severe CRS (grade 4). Therefore, consideration should be given to monitoring cardiac function by cardiac 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 or 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 6-2.

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

Table 6-1 CRS management algorithm:

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Mild symptoms requiring symptomatic treatment only e.g. low fever, fatigue, anorexia, etc.	Exclude other causes (e.g. infection) and treat specific symptoms with e.g. antipyretics, anti-emetics, anti-analgesics, etc. If neutropenic, administer antibiotics per local guidelines	Not applicable	Not applicable
Symptoms requiring moderate intervention:	Antipyretics, oxygen, intravenous fluids and/or low dose	If no improvement after symptomatic treatment	If no improvement within 12-18 hours of tocilizumab, administer

[redacted]

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

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

Table 6-2 CTL019-therapy-associated grading for cytokine release syndrome: (Lee et al 2014) - further Amendment 6

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

[redacted]

Grade	Toxicity
Grade 5	Death

*High dose vasopressor doses are shown in Table 6-3

Table 6-3 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 VASST formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 mcg/min (using VASST formula)
VASST Trial Vasopressor 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). **Note:** Pediatric weight adjustments should be taken into consideration	

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 three days prior to or following CTL019 infusion.
  - Uric acid ≥ 8 mg/dL or 25% increase from baseline
  - Potassium ≥ 6 mEq/L or 25% increase from baseline
  - Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline
  - Calcium ≤ 7 mg/dL or 25% decrease from baseline

[redacted]

- 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
- 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 the age-adjusted 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).

Graft-Versus-Host Disease (GVHD)

The chance of GVHD occurring is low, but it is a potential risk with CTL019 therapy. A prior study of activated donor lymphocyte infusions (*ex vivo* activated cells collected from the donor and grown in the same fashion as CTL019 but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4) (Porter et al 2006). Ten ALL patients have been treated to date with autologous CTL019 therapy who have had prior allogeneic hematopoietic SCT with residual donor chimerism. None of these patients developed GVHD after CTL019 infusion.

As part of the exclusion criteria for this protocol regarding GVHD, the grading & staging assessment of acute GVHD will follow the criteria described below in Table 6-4, and the definition of chronic GVHD will follow the criteria described in Table 6-5.

Table 6-4 Staging and grading of acute Graft-Versus-Host Disease

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

[redacted]

Extent of organ involvement			
	Skin	**Liver**	**Gut**
IV[f]	Stage 4 or	Stage 4	

a. Use "rule of nines" or burn chart to determine extent of rash.
b. Range given as total bilirubin. Downgrade by 1 stage if an additional cause of elevated bilirubin has been documented.
c. Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Gut staging for pediatric patients was not discussed at the Consensus Conference. Downgrade by 1 stage if an additional cause of diarrhea has been documented.
d. Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.
e. Criteria for grading given as a minimum degree of organ involvement required to confer that grade.
f. Grade IV may also include lesser organ involvement but with extreme decrease in performance status.

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

Table 6-5 Definitions of chronic Graft-Versus-Host Disease

Definite and Possible Manifestations of Chronic GVHD		
Organ System	**Definite Manifestations of Chronic GVHD**	**Possible Manifestations of Chronic GVHD**
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia	Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis	Xerostomia, keratoconjunctivitis sicca
Gastrointestinal (GI) tract	Esophageal strictures, steatorrhea	Anorexia, malabsorption, weight loss, diarrhea, abdominal pain
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubinemia
Genitourinary (GU)	Vaginal stricture, lichen planus	Non-infectious vaginitis, vaginal atrophy
Musculo-skeletal/ Serosa	Non-specific arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization	Arthralgia
Hematologic	None	Thrombocytopenia, eosinophilia, autoimmune cytopenias
Lung	Bronchiolitis obliterans	Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis

1. At any time point post-transplant, if there are ANY definite symptoms (column 2) then the symptoms should be identified as chronic GVHD.
2. At any time point post-transplant, if there are any possible symptoms (column 3) but no definite symptoms, then it is at the physicians' discretion to identify as either acute or chronic GVHD.
3. Acute and chronic GVHD cannot be present at the same time. Thus if #1 is fulfilled, then all manifestations of GVHD should be identified as chronic GVHD.

[redacted]

Limited Chronic GVHD

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

Extensive Chronic GVHD

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

B cell depletion

Depletion of B cells with resulting hypogammaglobulinemia is expected as a result of CTL019 on target effects in patient with sustained tumor response. 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 their value negligible.

Other potential complications of B cell aplasia include progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B virus. Neither PML nor reactivation of hepatitis B virus have been seen yet with CTL019; however, other therapies associated with B cell aplasia have seen these complications.

For the first 12 months following CTL019 infusion, data on all significant infections will be collected for patients in the primary follow-up. After 12 months following CTL019 infusion or if patients move to the secondary follow-up prior to month 12, 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

[redacted]

6.2.4.3 Potential toxicities

Replication-competent lentivirus (RCL)

An RCL may be generated during CTL019 manufacturing or subsequently after introduction of vector transduced cells into the patient. However, an RCL resulting from manufacturing is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL before it can be released to a patient. Thus patients will only receive cell products that meet RCL release criteria. Nevertheless, generation of an RCL following infusion of the vector product remains a theoretical possibility. The development of RCL could pose a risk to both the patient and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial (see [Laboratory 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. If a positive RCL assay result is obtained from a patient blood specimen, (as detected by Vesicular Stomatitis Virus/Glycoprotein (VSV-G) q-PCR, for example) the Investigator will be informed and the patient rescheduled for a retest of the DNA test. Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a patient. However, because the probability and characteristics of an RCL are unknown, no guidelines have been put in place. Nevertheless, all agree that the patient must be isolated until an understanding of how to manage the patient becomes clear. Some considerations are:

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

Clonality and insertional oncogenesis

The occurrence of adverse events caused by insertional mutagenesis in three patients in a gene therapy trial for X-linked Severe Combined Immunodeficiency (SCID) following stem cell therapy emphasizes the potential for problems in translating this approach to the clinic. To date, clinically evident insertional mutagenesis has not been reported following adoptive infusion of engineered T cells. Lentiviral vectors may have a lower risk than oncoretroviral vectors based on several considerations. Monitoring for T cell clonal outgrowth will be performed by q-PCR quantitation of the CTL019 transgene, and by complete blood count (CBC). If monoclonality is found, further studies including insertion site analysis will be considered.

Uncontrolled T cell proliferation

CTL019 transduced cells could theoretically proliferate without the control of normal homeostatic mechanisms. In pre-clinical studies (Milone et al 2009) and clinical experience to date (Porter 2011, Grupp 2013), CTL019 transduced 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 beneficial or harmful depending on the

[redacted]

extent of proliferation. Clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials (Dudley 2002, Dudley 2005).

If uncontrolled T cell proliferation occurs (e.g. expansion of T cells in the absence of CD19 antigen), patients may be treated with corticosteroids such as methylprednisolone (2 mg/kg/d i.v.) or chemotherapy, such as high dose cyclophosphamide. Investigators should further discuss this with the sponsor. Toxicity associated with allogeneic or autologous T cell infusions has been managed with a course of pharmacologic immunosuppression. T cell associated toxicity has been reported to respond to systemic corticosteroids (Lamers et al 2006). This theoretical toxicity is distinct from the toxicity associated with a CRS that develops during T cell proliferation upon exposure to CD19 expressing cells. CRS associated with T cell expansion is managed with anti-cytokine therapy, not immunosuppressants, and is addressed in Section 6.2.4.2.

Patients with CD19 CAR transgene levels [redacted]

[redacted]

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

Immunogenicity

Immunogenicity of the CAR polypeptide has been described in several studies (Park 2007, Lamers 2006, Lamers 2007, Lamers 2011) Host immune responses may result from presentation of CAR transgene expressed immunogenic epitopes including murine sequences in the scFV extracellular binding domain (derived from a murine monoclonal antibody) or novel epitopes arising at junctions between components of the CAR fusion polypeptide. Transgene and vector specific B and T cell immune responses have been previously observed in CAR modified autologous T cell therapies even when lymphodepleting regimens were used prior to infusion. If an immune response to the CTL019 cells occurs, it is possible that the cells might be rejected. Such immune responses could also have effects such as attenuating the responsiveness of CTL019 cells by causing an immune mediated deletion of the CTL019 cells. Six of 7 evaluable patients had evidence of human anti-CAR antibody directed to the murine monoclonal antibody derived scVF in CAIX specific CAR T therapy for renal cell carcinoma (Lamers et al 2011). A single patient experienced an anaphylactic reaction after multiple, repeated injections of a CAR with a murine based scFv (Maus et al 2013). Impaired function of CEA- targeting autologous T cells has been observed *in vitro* following exposure to receptor specific IgG obtained from treated patients. (Parkhurst et al 2011)

[redacted]

Immunogenicity (humoral and cellular) will be measured following CTL019 infusions as indicated in the Visit Evaluation Schedule.

Immunoglobulin depletion

Transient or permanent B cell depletion is a risk with CTL019 therapy, since normal B cells express CD19. This is expected to resolve if and when the CTL019 cells are cleared. Patients may require periodic infusions of immunoglobulin based upon local and age specific guidelines for specific patient populations.

Progressive multifocal leukoencephalopathy (PML)

PML is rare but well described with antibodies causing B cell aplasia (Weissert 2011) and is a demyelinating disease of the central nervous system, resulting from infection of oligodendrocytes and astrocytes, mostly with JC virus. PML classically has a subacute clinical presentation with focal neurologic deficits, such as weakness, speech difficulties, unsteady gait and hemiparesis. Ophthalmic symptoms are relatively common, occurring as homonymous hemianopia which progresses to cortical blindness. Seizure and headache are uncommon. Dementia manifesting as mental deficits in cognition, personality changes, and memory impairment are also common, but it is almost invariably associated with the focal neurologic deficits of PML. By CT or MRI radiographic assessment, lesions are confined to the white matter, most commonly of the occipitoparietal lobe and without mass effect.

In general, patients with known B cell aplasia are at increased risk for PML. Therefore patients in the study will be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

Hepatitis B reactivation

Reactivation of hepatitis B refers to the abrupt increase in hepatitis B virus (HBV) replication in a patient with inactive or resolved hepatitis B. Reactivation can occur spontaneously, but more typically is triggered by immunosuppressive therapy of cancer, autoimmune disease, or organ transplantation. Reactivation can be transient and clinically silent, but often causes a flare of disease that can be severe resulting in acute hepatic failure. Most instances of reactivation resolve spontaneously, but if immune suppression is continued, re-establishment of chronic hepatitis occurs which can lead to progressive liver injury and cirrhosis. Reactivation is defined as increase of one log in HBV-DNA relative to baseline HBV-DNA or new appearance of measurable HBV-DNA (Hoofnagle 2009). Patients with evidence of reactivated hepatitis B should initiate either tenofovir or entecavir, and pursue appropriate consultation.

In general, the risk of hepatitis B reactivation is increased in patients with B cell depletion. Patients with latent or active hepatitis B are typically excluded from CTL019 treatment protocols; however infection could potentially occur following the treatment trial completion or early withdrawal. Therefore, patients with a history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection. Standard guidelines should be followed for the treatment of active/reactivated hepatitis B (Hoofnagle 2009).

[redacted]

Individuals with evidence of prior unresolved or ongoing HBV infection (See Section 14.2, Table 14-4) are at increased risk of reactivation of HBV infection (Patel 2015) and are excluded from this study.

New or secondary malignancies

There is a theoretical concern that transduction of a patient's T-cells with CD19 CAR lentiviral vector could result in an oncogenic effect within these T-cells that could result in a T-cell leukemia or lymphoma.

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 will be collected for CAR-transgene and RCL testing.

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 exploratory analysis, such as CAR-transgene and RCL. Additional details for sample handling and shipping are outlined in the laboratory manual.

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 medications, excluding vitamins, 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, CRF Completion Guidelines (CCGs), and Table 6-6 below. Modified collection of concomitant medications during these trial phases 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.

Table 6-6 Concomitant medication reporting by trial phase

Trial phase	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:

[redacted]

- 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 until CRS is resolved. Long acting G-CSF should not be given within 10 days of CTL019 infusion and until CRS is resolved. The effects of granulocyte colony stimulating factor (G-CSF) 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 Table 6-1 and Section 6.2.4.2.

6.2.7 Prohibited concomitant therapy

Concurrent use of systemic steroids or immunosuppressant medications are prohibited under this protocol except as required for physiologic replacement of hydrocortisone, or in the case of a life threatening emergency, since this may have an adverse effect of CTL019 cell expansion and function.

Specifically, the following medications are excluded:

a. **Steroids:** Therapeutic systemic 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. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
c. **GVHD therapies:** Any systemic drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-TNF, anti-IL6 or anti-IL6R, systemic steroids)
d. **Chemotherapy:**
    - Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion
    - The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated)
    - The following drugs must be stopped > 2 weeks prior to CTL019 infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside > 100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs
    - Pegylated-asparaginase must be stopped > 4 weeks prior to CTL019 infusion

[redacted]

e. **CNS disease prophylaxis:**
   - CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)

f. **Radiotherapy:**
   - Non-CNS site of radiation must be completed > 2 weeks prior to CTL019 infusion
   - CNS directed radiation must be completed > 8 weeks prior to CTL019 infusion

g. **Anti T-cell Antibodies:** Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to CTL019 is prohibited since residual lytic levels may destroy the infused CTL019 cells and/or prevent their in vivo expansion. If such an agent has been administered within 8 weeks prior to CTL019, contact the Sponsor, consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.

6.3 Dose modifications

6.3.1 Dose modifications and dose delays

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 CTL019, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

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

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

Please refer to Table 14-6 in Appendix 7 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 14-5 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 14-6. Repeat liver chemistry tests (alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), prothrombin time and international normalized ratio (PT/INR), alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (G-GT) to confirm elevation.

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

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

[redacted]

- Discontinuation of the investigational drug, if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event, which can include based on investigator's discretion:
  - Serology tests, imaging (e.g., such as abdominal ultrasound (US), computed tomography scan (CT) or magnetic resonance imaging scan (MRI), as appropriate) and pathology assessments, gastroenterologist's or hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease, obtaining a history of exposure to environmental chemical agents.

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

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

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

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

- For patients with normal ALT or AST or TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN, or ALT or AST >5.0 x ULN in isolation.
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

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

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury).

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

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of alcohol consumption, illicit drug use, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

[redacted]

- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) such as a right upper quadrant (RUQ) ultrasound with duplex for flow, may be warranted.
- If bilirubin elevation is an isolated event (no transaminase elevations above baseline is seen), then a work-up for hemolysis is appropriate (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin).
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.2.3 Renal safety monitoring

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

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

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

Every renal laboratory trigger or renal event as defined in Table 14-7 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 14-8 (Appendix 8)

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Upon informed consent/assent completion, the patient will initiate screening. Each patient is identified in the study by a seven digit Subject Number (Subject No.), that is assigned sequentially at each site by the site investigator or designated staff when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the four digit Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential three digit patient number suffixed to it, such that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle RDC interface.

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

[redacted]

not be reused for any other patient 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 documented and entered onto the appropriate CRF page.

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, and receipt and acceptance of the apheresed product by the manufacturing facility.

6.4.3 Treatment blinding

This is an open-label study.

6.5 Study drug preparation and dispensation

Upon release from the manufacturing facility, the cryopreserved CTL019 cell product is shipped to the investigator. Upon receipt of the cryopreserved CTL019 cell product, inventory must be performed. The respective drug receipt form is completed and signed by personnel accepting the shipment of CTL019. It is important that the designated study staff verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable CTL019 cell product in a given shipment will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable CTL019 cell product that was supplied to the investigator's site.

The CTL019 cell product will remain in storage until the subject is available for infusion and ready (Section 6.5.2). Please note the time between product thawing and completion of the infusion should not exceed 30 minutes to maintain maximum product viability. Therefore, to ensure this timeframe, the product should be thawed in close proximity to the patient's bedside. Additionally, after cell thawing the CTL019 cell product should **NOT** be washed prior to infusion. All contents must be infused. If the CTL019 cell product appears to have a damaged or leaking bag, or otherwise appears to be compromised, it should not be infused, and should be disposed of according to local institutional standard operating procedures.

For further details on product receipt, storage, preparation, and administration, see Section 6.1.1.2 and the [Investigational Product Handling Manual] (e.g. option of syringe-based administration for pediatric patients with small product volumes).

6.5.1 Study drug packaging and labeling

Each infusion bag will typically contain 10 – 50 mL of cells containing a cell dose of 0.2 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). Higher volumes may occasionally be necessary depending on transduction efficiency.

Each infusion bag will have affixed to it a label containing the following: A product identifier, the proper name of the product, and appropriate product modifiers and attributes according to the International Standard for Blood and Transplant (ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Description, Version 4.28). The study number and the wording "FOR AUTOLOGOUS USE ONLY" will be included in the label. In addition the

[redacted]

label will have at least two unique identifiers such as the patient's alphanumeric identifier and birth date according to applicable regulations. Additional label elements required by local regulatory guidelines will also be included. Prior to the infusion, two individuals will verify all of this information and confirm identity according to local institutional guidelines, to ensure that the information is correctly matched to the patient, and that the patient receives only their autologous product.

6.5.2 Drug supply and storage

CTL019 cell product must be received, handled and stored safely and properly by designated personnel at the study site, CTL019 must be kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the CTL019 cell product should be stored according to the instructions specified on the product labels and in the [Investigational Product Handling Manual].

6.5.3 Study drug compliance and accountability

Novartis has established methods to ensure full traceability between the patient's autologous apheresis and the CTL019 product in line with the requirements outlined in 21 CFR1271.250, 21CFR1271.290, Regulation (EC) 1394/2007, the Directive 2004/23/EC as well as the rules and principles of the EU "Detailed guidelines on good clinical practice specific to advanced therapy medicinal products." The data contributing to the full traceability of the cells are stored for a minimum of 30 years. Any product quality complaints are documented by the clinical site and reported to the Novartis Clinical Supplies Quality Assurance (QA) Department. A unique patient identifier will be used in order to maintain the chain of identity between the autologous apheresis product and the CTL019 batch, and the link between patient identity and unique patient identifier will be confirmed prior to infusion. The [Investigational Product Handling Manual], [Leukapheresis, Cryopreservation & Scheduling Manual], and [Investigational Product Transport Manual] provides an overview of how the company ensures that the cells which are procured, processed, stored, and distributed by or on behalf of the Novartis can be traced from donor to recipient and vice versa.

6.5.3.1 Study drug compliance

As a single administration study, compliance will be assessed by the investigator and/or study personnel and captured on site infusion records and drug accountability records.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of CTL019 cell product in a drug accountability log. Drug accountability records will be reviewed by the field monitor during site visits and at the completion of the study.

6.5.3.3 Handling of other study treatment

Not applicable.

[redacted]

6.5.4 Disposal and destruction

CTL019 cell product may require disposal for a variety of reasons, including but not limited to: 1) Mislabeled product; 2) Condition of patient prohibits infusion, and/or 3) Patient refuses infusion. Disposal of unused CTL019 product must be approved by Novartis study team. Upon Novartis's approval, CTL019 may be disposed of according to local laws/ institutional standard operating procedures (SOP).

Any unused product and all used infusion supplies, including the infusion bag and tubing, must be disposed of according to local institutional standard operating procedures. For further details, please refer to the specific guidance provided in the [Investigational Product Handling Manual].

Reconciliation of CTL019 cell product shipped, consumed, and remaining, is performed by Novartis (or designee). All CTL019 cell product disposition will be documented in the study files.

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 7.1.3).

For patients who discontinue early from the Treatment and Primary Follow-Up Phase prior to Month 60, the patient will enter a 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 since CTL019 infusion when the patient discontinued from the Treatment and Primary Follow-Up Phase. 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). It is anticipated that patients may leave the primary follow-up and move to secondary follow-up due to reasons including: treatment failure, relapse after remission, pursuing SCT while in remission, or withdrawal from the primary follow-up (See Figure 7-1 below).

In each table, required assessments are indicated with an "X", and the visits when they are performed. The letter (D) 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 as a source document.

[redacted]

Figure 7-1 Potential patient flow scenarios

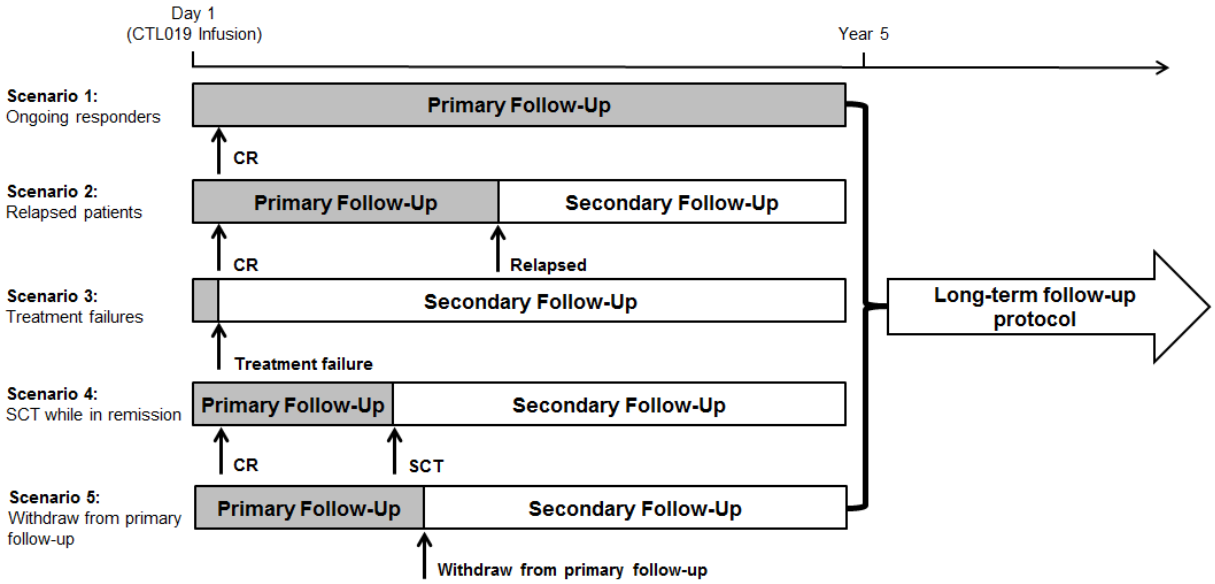


Table 7-1 Visit evaluation schedule: treatment and primary follow-up

Phase			**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name	**Category**	**Protocol Reference Section**	**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Obtain Informed Consent/Assent	D	11.3.	X																		
IWRS/IRT	S	7.1.1.1.	X	X			X		X	X	X	X		X	X	X M3 & M6 only	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																		
Diagnosis and extent of cancer	D	7.1.1.	X																		
Cytogenetics/FISH/Tumor Immunophenotyping	D	7.1.1.	X																		

[redacted]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up															Survival Follow-up
Visit Name			Screening	Enrollment/Pre-chemotherapy	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post infusion													End of Treatment & Primary Follow-up	Survival Follow-up After study completion
Study Day			W-16 to W-12	W-16 to D-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±4d	M2 M3 M4 M5 M6 ±14d	M9 M12 ±14d	M15 M18 M21 ±14d	M24 M36 M48 ±14d	M30 M42 M54 ±14d	M60 ±14d	q3m ±14d
Prior antineoplastic therapy	D	7.1.1.	X																			
Donor chimerism (prior allogeneic SCT patients only, or if unknown)	D	6.2.4.2. 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	X	X	X	X	
Physical examination (PE)	S	7.2.1.1.	X			X		X		X		X		X	X	X	X	X	X	X	X	
Performance status assessment	D	7.2.2.3.	X			X		X		X		X		X	X	X	X	X	X	X	X	
Height	D	7.2.2.2.	X													X M6 only	X M12 only	X M18 only	X	X	X	
Tanner staging (only for patients < 18 years old)	D	7.2.2.	X													X M6 only	X M12 only	X M18 only	X	X	X	

[redacted]

Phase			**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name	**Category**	**Protocol Reference Section**	**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Weight	D	7.2.2.2.	X			X									X	X M3 & M6 only	X	X M18 only	X	X	X	
Vital signs	D	7.2.2.1.	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PedsQL and EQ-5D Questionnaire	D	7.2.7.		X											X	X M3 & M6 only	X	X M18 only	X		X	
Hospitalization status	D	7.2.6.	Hospitalizations from Screening to Month 2																			
Intervention																						
Leukapheresis/Apheresis	D	4.1.1	X																			
Leukapheresis/Apheresis pre-evaluation and acceptance	D	4.1.1	X																			
Lymphodepleting Chemotherapy	D	6.1.1.1.			X																	
Other chemotherapy while on study	D	6.2.6.	As clinically indicated																			

[redacted]

Phase			**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name	**Category**	**Protocol Reference Section**	**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
CTL019 infusion prerequisite assessment	S	6.1.1.2.					X														
CTL019 T cell infusion	D	6.1.1.2.					X														
Antineoplastic therapies after CTL019 infusion or study discontinuation	D	6.2.6.						X	X	X	X	X	X	X	X	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	
Lab tests of special interest during CRS only (CRP, ferritin, fibrinogen, LDH, PT, aPTT, INR, D-dimer)	D	7.2.2.5.					X	X	X	X	X	X	X	X	X							
Serum pregnancy test	D	7.2.2.5.	X		X	X																

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Serum or Urine pregnancy test	S	7.2.2.5													X (Serum or Urine)	X (Serum or Urine)	X Serum or Urine)	X (Serum or Urine)	X (Serum or Urine)	X (Serum or Urine)	X (Serum)	
HIV Test	D	7.2.2.5.	X																			
Hepatitis B and C	D	7.2.2.5.	X																			
Influenza A and B	D	6.1.1.2. 7.1.2.		Within 10 days of infusion																		
Coagulation factors (PT, aPTT, INR, fibrinogen, D-dimer)	D	7.2.2.5.	X		X		X			X		X			X							
Serum immunoglobulin levels (IgG, IgA, IgM)	D	7.2.2.5.	X									X			X	X M3 & M6 only	X					
MUGA/ECHO	D	7.1.1.	X																			
Electrocardiogram (ECG)	D	7.1.1.	X				X															
Urinalysis	D	7.2.2.5.	X																			

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Pulse oximetry	D	7.2.2.1.	X				X														
Disease Assessments																					
Bone Marrow biopsy and aspirate morphology	D	7.2.1.	X												X	If patient is not in CR/CRi at D28, then **required** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						
EOI local MRD assessment in bone marrow aspirate	D	7.2.1	X																		
MRD assessment in bone marrow aspirate by flow cytometry (includes normal B cell counts and CD19 status)	D	7.2.1.	X												X	If patient is not in CR/CRi at D28, then **required** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						
MRD assessment in bone marrow aspirate by qPCR	D	7.2.1.	X												X	If patient is not in CR/CRi at D28, then **required** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						

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Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Tumor cell assessment by flow cytometry of peripheral blood (includes normal B cell counts and CD19 status)	D	7.2.1.	X							X		X		X	X	X M3 & M6 only	X	X M18 only	X	X	X	
Lymph node or other involved tissue aspirate or biopsy	D	7.2.1.	As clinically indicated																			
CSF assessment by lumbar puncture	D	7.2.1.	X												X	If patient is not in CR/CRi at D28, then **required** at the first time clinical evidence of remission is seen by blood and PE. Otherwise, as clinically indicated by the presence of neurologic symptoms.						
CNS Brain Imaging (MRI/CT)	S	7.2.1.	As clinically indicated																			
Extramedullary disease assessment (physical exam and CNS symptom assessment)	D	7.2.1.1. 7.2.1.2.	X												X	X	X	X	X	X	X	

[redacted]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up														Survival Follow-up
Visit Name			Screening	Enrollment/Pre-chemotherapy	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post infusion												End of Treatment & Primary Follow-up	Survival Follow-up After study completion
Study Day			W-16 to W-12	W-16 to D-1	D-14 to D-2	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17 ±3d	D21 ±3d	D28 ±4d	M2 M3 M4 M5 M6 ±14d	M9 M12 ±14d	M15 M18 M21 ±14d	M24 M36 M48 ±14d	M30 M42 M54 ±14d	M60 ±14d	q3m ±14d
Safety																					
Adverse events	D	8.1.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancies and menstrual status	S	7.2.2. 7.2.2.5	X	X												X	X	X	X	X	X	
Immunogenicity (serum)	D	7.2.2.5. 10.5.3.4.		X								X			X	X M3 & M6 only	X M12 only	X M24 only (Cohort 1 and Cohort 2) If patient relapses at any time point (before or after Month 24), then immunogenicity sample collection required at relapse visit.				
Immunogenicity (peripheral blood)	D	7.2.2.4. 10.5.3.4.		X								X			X	X M3 & M6 only	X M12 only	X M24 only (Cohort 1 and Cohort 2) If patient relapses at any time point (before or after Month 24), then immunogenicity sample collection required at relapse visit.				

[redacted]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up														Survival Follow-up
Visit Name			Screening	Enrollment/Pre-chemotherapy	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post infusion												End of Treatment & Primary Follow-up	Survival Follow-up After study completion
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
RCL by VSV-G q-PCR (peripheral blood)	D	6.2.4.3.		X												X M3 & M6 only	X M12 only		X		X	
Biomarkers																						
Cytokines (serum)	D	7.2.4.		X			X	X	X	X		X		X	X	X M3 & M6 only	X M12 only					
CRS assessments by peripheral blood (anti-cytokine therapy PK, CTL019 PK, cytokines, IL-6R and inflammatory markers)	D	7.1.3.					As clinically indicated dependent upon the presence and time-course of CRS and administration of anti-cytokine therapies – refer to Table 7-7, Table 7-8, Table 7-15, Table 7-16, Table 7-17.															
CTL019 pharmacokinetics by q-PCR (peripheral blood)	D	7.2.3.		X			X		X	X	X	X		X	X	X M3 & M6 only	X	X M18 only	X	X	X	

[redacted]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up														Survival Follow-up
Visit Name			Screening	Enrollment/Pre-chemotherapy	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post infusion												End of Treatment & Primary Follow-up	Survival Follow-up After study completion
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
CTL019 pharmacokinetics and normal T cells by flow cytometry (peripheral blood)	D	7.2.3.		X					X	X	X	X		X	X	X M3 & M6 only	X	X M18 only	X	X	X	
CTL019 pharmacokinetics by q-PCR (bone marrow aspirate)	D	7.2.3.	X												X	If patient is not in CR/CRi at D28, then **recommended** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						
CTL019 pharmacokinetics by flow cytometry (bone marrow aspirate)	D	7.2.3.	X												X	If patient is not in CR/CRi at D28, then **recommended** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						
CTL019 pharmacokinetics by q-PCR (CSF)	D	7.2.3.	X												X	If patient is not in CR/CRi at D28, then **recommended** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						

[redacted]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up														Survival Follow-up
Visit Name			Screening	Enrollment/Pre-chemotherapy	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post infusion												End of Treatment & Primary Follow-up	Survival Follow-up After study completion
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
CTL019 Immunophenotyping by flow cytometry (peripheral blood)	D	7.2.4.		X						X		X		X	X	X M3 & M6 only	X		X M24 & M36 only			
[redacted]																					

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Apheresis sample for correlative studies	D	7.2.4.		X																	
CTL019 cell product sample for correlative studies	D	7.2.4.		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			X														X	

[redacted]

Table 7-2 Visit evaluation schedule: secondary follow-up

For patients who end their primary follow-up before month 60:

Phase	**Category**	**Protocol Reference Section**	**Secondary Follow-up**									**Survival Follow-up**
Visit Name			**Post Infusion**								**End of Secondary Follow-up**	**Survival Follow-up after study completion**
Study Day			**M2 ±14d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±14d**	**M24 ±14d**	**M36 ±14d**	**M48 ±14d**	**M60 ±14d**	**q3m ±14d**
Patient History												
Concomitant medications (selected)	D	7.1.4.1.					X	X	X	X	X	
First antineoplastic therapy after CTL019 infusion (only for patients in remission)	D	7.1.4.	For all patients who are in remission, the first antineoplastic therapy administered (first therapy including conditioning for cell therapy (CAR, SCT) plus cell therapy (CAR, SCT) should be reported.									
Height	D	7.2.2.2.					X	X	X	X	X	
Weight	D	7.2.2.2.					X	X	X	X	X	
Tanner staging (only for patients < 18 years old)	D	7.2.2.					X	X	X	X	X	
Efficacy assessments												
Relapse information (only for patients in remission)	D	7.1.4.	For all patients who are in remission, relapse status should be assessed every 3 months until first relapse (if applicable). If a patient misses an annual scheduled visit where relapse status is required, or if the time-point does not align with a scheduled visit, relapse status can be obtained remotely.									
Safety assessments												
Protocol defined adverse events, including new malignancies and significant findings	D	7.1.4.	Protocol defined adverse events should be reported upon investigator knowledge which may not align with scheduled visits.									
Serum or Urine pregnancy Test	S	7.2.2.5	X (serum or urine)	X (serum or urine)	X (serum or urine)	X (serum or urine)	X (serum or urine)	X (serum or urine)	X (serum or urine)	X (serum or urine)	X (serum)	

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Secondary Follow-up**									**Survival Follow-up**
Visit Name			**Post Infusion**								**End of Secondary Follow-up**	**Survival Follow-up after study completion**
Study Day			**M2 ±14d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±14d**	**M24 ±14d**	**M36 ±14d**	**M48 ±14d**	**M60 ±14d**	**q3m ±14d**
Pregnancies and menstrual status	D	7.2.2.					X	X	X	X	X	
Hematology	S	7.2.2.5.					X	X	X	X	X	
Physical examination (PE)	S	7.2.1.1.					X	X	X	X	X	
CTL019 transgene persistence (peripheral blood)	D	7.2.3.		X	X	X	X	X	X	X	X	
Flow Cytometry of peripheral blood (B cell, T cell levels	D	7.2.1.		X	X	X	X	X	X	X	X	
RCL by VSV-G q-PCR (peripheral blood)	D	6.2.4.3.		X	X		X	X	X	X	X	
Immunogenicity (serum)	D	7.2.2.5. 10.5.3.4.		X	X		X	X (Cohort 1 and Cohort 2)				
Immunogenicity (peripheral blood)	D	7.2.2.4. 10.5.3.4.		X	X		X	X (Cohort 1 and Cohort 2)				
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

Anti-microbial prophylaxis treatment in these immunosuppressant relapsed/refractory ALL patients should be considered per local institutional guidelines at study entry or prior to lymphodepleting chemotherapy.

Only following confirmation of all clinical eligibility criteria (defined as all inclusion/exclusion criteria except that which pertains to the leukapheresis product) will the patient's leukapheresis product be shipped to the manufacturing facility. The manufacturing facility will then evaluate the patient's leukapheresis product for acceptance.

Patients should not be enrolled if they are unwilling to be followed up long-term i.e. 15 year follow up as required by the health authorities for cell and gene therapy products.

CTL019 infusion should occur within 16 weeks of informed consent.

Patients who have signed an informed consent/assent will undergo a routine leukemia staging workup including:

a. Demography
b. Medical history (including diagnosis and extent of cancer and any prior history of CNS leukemia involvement) and prior/concomitant medications and antineoplastic therapies
c. Physical Examination (PE) including height, weight, GVHD assessment, Tanner staging (only for patients < 18 years old), vital signs, extramedullary disease assessment and CNS symptom assessment
d. Performance status (Karnofsky [age ≥16 years] or Lansky [age < 16 years]) at the time of screening
e. Standard ALL cytogenetics, FISH, and tumor immunophenotyping by flow cytometry analysis required (at the time of most recent relapse). If not available, test must be performed at screening.
f. Donor Chimerism (within 3 months of screening, prior allogeneic SCT patients only, or if unknown)
g. Complete Blood Count, Differential
h. Chemistry Panel
i. Coagulation panel
j. Urinalysis
k. Serum pregnancy test (if WOCBP)
l. HIV Testing (test within 8 weeks of screening) – If an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines
m. Hepatitis B and Hepatitis C test (test within 8 weeks of screening; see Appendix 2 for interpretation of Hepatitis B results)
n. Serum immunoglobulin levels (IgG, IgA, IgM)
o. MUGA or ECHO (performed within 6 weeks of infusion) for LVSF/LVEF
p. ECG
q. Pulse oximetry
r. Bone marrow aspirate and biopsy for:

[redacted]

- Morphologic blast enumeration
- Flow cytometry (B-cell numbers, tumor cell numbers, MRD assessment (including Local Assessment with protocol amendment 6 at EOI), CD19 assessment, and CTL019 immunophenotyping)
  - CTL019 PK (qPCR and flow cytometry)
  - [redacted]

s. Peripheral blood collection for flow cytometry (B and T-cell numbers, tumor cell numbers, and CD19 assessment)
t. Lymph node or tissue aspirate or biopsy (if clinically indicated)
u. Lumbar Puncture (LP) for CSF cytologic assessment and CTL019 PK (by q-PCR)
v. CNS Brain Imaging (MRI/CT) (if clinically indicated)
w. Adverse events

7.1.1.1 Eligibility screening and enrollment

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

Once clinical eligibility has been confirmed, only then can the patient's apheresis product be shipped to the manufacturing facility. The manufacturing facility will then evaluate the patient's apheresis product for acceptance and notify the site. Enrollment is defined as the point at which a patient meets all clinical inclusion/exclusion criteria and the patient's apheresis product is received and accepted by the manufacturing facility. 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.

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.

7.1.1.2 Information to be collected on screening failures

The reason for not being enrolled will be entered in the clinical database. The demographic information, informed consent/assent, Inclusion/Exclusion pages, any adverse events leading to subject discontinuation, and any adverse events that meet reporting criteria in Appendix 3: CTL019 Modified Data Reporting 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.

[redacted]

Enrollment/Pre-chemotherapy evaluation visit (W-16 to D-1)

Before the scheduled lymphodepleting chemotherapy regimen is to begin, the patient will undergo blood collection for safety and biomarker assessments (including CTL019 PK, immunophenotyping [redacted] humoral & cellular immunogenicity and RCL by VSV-G qPCR). These draws can be collected at any time after informed consent is signed up until before the lymphodepleting chemotherapy is scheduled. In addition, adverse events and prior/concomitant medications will be reviewed. Viably frozen samples from the leukapheresis material as well as the CTL019 product will be collected at the manufacturing site for correlative studies. In addition, the Patient Reported Outcome questionnaires should be completed at the time of enrollment. Under extenuating circumstances where the baseline PRO questionnaire(s) was not completed at enrollment, it must be completed before the administration of LD chemotherapy or the CTL019 infusion if LD chemotherapy is not administered.

Lymphodepleting chemotherapy visit (D-14 to D-2)

It is anticipated that many patients will have been receiving chemotherapy for relapse or resistant disease. For inclusion they will have responding or stable disease to the most recent therapy. Prior to CTL019 cell infusion and after leukapheresis, an additional chemotherapy cycle is planned. Patients referred with stable disease on no recent therapy will be eligible as well. The use of additional chemotherapy prior to the recommended preinfusion chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden. In addition for patients in Cohort 1 and Cohort 2, serum pregnancy test will be performed on WOCBP confirming a negative pregnancy result.

When given, lymphodepleting chemotherapy should be started before CTL019 infusion so that these cells will be given 2 to 14 days after completion of the lymphodepleting chemotherapy. The timing of chemotherapy initiation therefore depends on the length of the regimen. The purpose of the chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CTL019 cells. Fludarabine (30 mg/m^2 i.v. daily for 4 doses) and cyclophosphamide (500 mg/m^2 i.v. daily for 2 doses starting with the first dose of fludarabine) 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.

If patients have a WBC count ≤ 1,000 cells/μL within one week prior to CTL019 infusion, lymphodepleting chemotherapy is **NOT** required. If the time between lymphodepleting chemotherapy and CTL019 infusion exceeds **4 weeks**, lymphodepleting chemotherapy will be repeated **only** if the patients WBC count is >1,000 cells/μL.

Patients will also undergo blood tests including chemistry, a coagulation panel, and a CBC with differential. In addition, adverse events and prior/concomitant medications will be reviewed.

Pre-infusion visit (D-1 +1d)

On the day prior to or day of the scheduled CTL019 infusion, patients will undergo a physical exam (including weight and vital signs) and a performance status assessment (Karnofsky (age ≥16 years) or Lansky (age < 16 years). In addition, serum pregnancy test will be performed on

[redacted]

WOCBP confirming a negative pregnancy result. In addition, adverse events and prior/concomitant medications will be reviewed.

Note: 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, he/she should complete a full course of oseltamivir phosphate or zanamivir as described in the label (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their full course of treatment **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 may need to be considered.

7.1.3 Treatment and Primary Follow-Up Phase

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

Infusion visit (D1)

CTL019 infusions will begin 2 to 14 days after lymphodepleting chemotherapy completion and within 16 weeks after obtaining informed consent. The time elapsed from informed consent to enrollment should not exceed 4 weeks, and enrollment to infusion should not exceed 12 weeks. The total window between informed consent and CTL019 infusion must not exceed 16 weeks. If this window exceeds 16 weeks, the case must be discussed and approved by the Sponsor in order to allow for CTL019 product to be infused.

The day of (but prior to) the CTL019 infusion, patients will undergo blood tests including chemistry, a CBC with differential, a coagulation panel and serum cytokines. 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 of 0.2 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). Vital signs will be monitored before and following CTL019 infusion (per Section 6.1.1.2). Blood samples 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.

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.

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

At the intervals following infusion listed above, patients will undergo one or more of the following: blood tests including chemistry, lab tests of special interest during CRS only (CRP, ferritin, fibrinogen, LDH, PT, aPTT, INR, D-dimer), hematology, coagulation, serum

[redacted]

immunoglobulin, humoral & cellular immunogenicity, serum cytokines, CTL019 PK, immunophenotyping, flow cytometry (B and T cells, tumor cells and CD19 assessment), a physical exam (with vital signs) and performance status assessment. In addition, adverse events and prior/concomitant medications will be reviewed. On Day 2, only vital signs, physical examination, a performance status assessment, serum cytokines, hematology, and chemistry (inclusive of LFTs and creatinine) will be performed.

Sample collections for serum cytokines, CTL019 PK, and inflammatory markers (e.g. ferritin and CRP) 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 that might better parallel these individual differences may also be collected as needed, if it is clinically feasible. Frequent monitoring of serum CRP, ferritin, and cytokines should be considered during the clinical course of CRS of any severity (e.g. every day to several days) especially around the following clinical events: initial persistence of fevers, hemodynamic instability, initial and worsening of respiratory distress, rapid clinical deterioration, just prior to and daily for 2 days following tocilizumab administration, around other clinically significant events and upon the clinical resolution of CRS.

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

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

Post-infusion visit (D28 ±4d)

Patients will undergo blood collection for hematology, chemistry, lab tests of special interest during CRS only (CRP, ferritin, fibrinogen, LDH, PT, aPTT, INR, D-dimer), coagulation, serum immunoglobulins, cytokines, flow cytometry (B and T cells, tumor cells, and CD19 assessment) humoral and cellular immunogenicity, CTL019 PK, immunophenotyping [redacted] Patients will have a lumbar puncture for CSF cytologic assessments and CTL019 PK. Patients are required to have a bone marrow biopsy and aspirate for morphology, flow cytometry, MRD, CTL019 PK [redacted]. In addition, patients will undergo a physical exam (including vital signs, weight, and extramedullary disease assessment), CNS symptom assessments and a performance status assessment. Tumor response assessments will be conducted (see Appendix 1 for response guidelines). A lymph node or tissue aspirate or biopsy may be done if clinically indicated. Adverse events and prior/concomitant medications will be reviewed. Serum or urine pregnancy test will be done for WOCBP until contraception is no longer required (see exclusion criteria #20).

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

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 and T cells, tumor cells, and CD19 assessment), cytokines, humoral & cellular immunogenicity and CTL019 PK, immunophenotyping, [redacted], and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including vital signs, height, weight, Tanner staging (only for patients < 18 years old), and extramedullary disease

[redacted]

assessment), CNS symptom assessment, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Serum or urine pregnancy test will be done for WOCBP until contraception is no longer required (see exclusion criteria #20).

Following initial achievement of CR or CRi, peripheral blood and extramedullary disease assessments (physical exam and CNS symptom assessment) should be performed at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi.

If patients were not in CR or CRi at the D28 visit assessment, a bone marrow biopsy/aspirate and CSF assessment/lumbar puncture will be required for tumor response assessments at the first visit where clinical evidence of remission is observed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessments).

Patients may also have a bone marrow biopsy, aspirate, LP/CSF assessment and lymph node aspirate or biopsy (if accessible) at month 3 and month 6 for tumor response assessments (recommended but not required).

For details of assessments at each 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, flow cytometry (B and T cells, tumor cells, and CD19 assessment), and CTL019 PK. In addition, patients will undergo a physical exam (including vital signs and extramedullary disease assessment), CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Serum or urine pregnancy test will be done for WOCBP until contraception is no longer required (see exclusion criteria #20).

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 and T cells, tumor cells, and CD19 assessment), cytokines, humoral and cellular immunogenicity, CTL019 PK, immunophenotyping, [redacted] and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including height, weight, GVHD assessment, Tanner staging (only for patients < 18 years old), vital signs, and extramedullary disease assessment), CNS symptom assessment, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Serum or urine pregnancy test will be done for WOCBP until contraception is no longer required (see exclusion criteria #20).

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

Patients with CD19 CAR transgene levels [redacted]

Identified vector integration sites will be evaluated using bioinformatic approaches to determine

[redacted]

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

Post-infusion visit (M15 ±14d, M18 ±14d, M21 ±14d)

Patients will undergo the following: blood collection for hematology, chemistry and CTL019 PK. Blood will be collected for flow cytometry (B and T cells, tumor cells) at M18 only. In addition, patients will undergo a physical exam (including height, weight and Tanner staging at M18 only), vital signs, extramedullary disease assessment, CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported. Serum or urine pregnancy test will be done for WOCBP until contraception is no longer required (see exclusion criteria #20).

Post-infusion visit (M24 ±14d, M30 ±14d, M36 ±14d, M42 ±14d, M48 ±14d, M54 ±14d)

Patients will undergo the following: blood collection for hematology, chemistry and CTL019 PK. Blood will be collected for flow cytometry (B and T cells, tumor cells) and RCL by VSV-G qPCR annually at M24, M36 and M48 only. If RCL testing was negative through Month 12, all samples taken after Month 12 will be stored for potential future testing. Blood will be collected for CTL019 immunophenotyping. In addition, patients will undergo a physical exam [including height, weight and Tanner staging (only for patients < 18 years old)], vital signs, extramedullary disease assessment, CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. 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, 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. Serum or urine pregnancy test will be done for WOCBP until contraception is no longer required (see exclusion criteria #20).

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 study.

During the End of Treatment and Primary Follow-Up visit, patients will undergo the following: blood collection for hematology, chemistry, CTL019 PK, flow cytometry (B and T cells, tumor cells) and RCL by VSV-G qPCR. If RCL testing was negative through Month 12, all samples taken after Month 12 will be stored for potential future testing. In addition, patients will

[redacted]

undergo a physical exam [including height, weight and Tanner staging (only for patients < 18 years old)], vital signs, extramedullary disease assessment, CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Serum pregnancy test will be performed on WOCBP confirming a negative pregnancy result. 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). Patients who discontinue or withdraw from the Treatment and Primary Follow-Up early 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. It is strongly recommended that patients that remain in remission be followed in the Treatment and Primary Follow-Up Phase for at least one year at a minimum at the treating investigational site to ensure adequate safety and efficacy data collection. 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:

- Treatment failure
- Relapse after remission
- Pursuing HSCT while in remission
- Patient voluntary withdrawal from the primary follow-up

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

* Does not want to participate in the study anymore, and

* Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient’s decision to withdraw his/her consent and record this information. No further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up. All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient’s study withdrawal should be made as detailed in the assessment table. Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient’s samples until their time of withdrawal) according to applicable law.

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

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

7.1.3.3 Relapse evaluation

If at any time during the Treatment and Primary Follow-Up phase following infusion, a patient who was in remission relapses, a full disease evaluation will be completed, if feasible. As soon as possible after awareness of a relapse, the patient will be scheduled for a visit, and will have a bone marrow biopsy & aspirate, and peripheral blood collection. The following assessments will be performed:

a. Tumor characterization: Can be done on either blood or bone marrow with known tumor involvement of these components depending on availability of specimens, but priority is to do the majority of testing on bone marrow:
   - Flow cytometry (B and T cells, tumor cells and CD19 assessment)
   - Blood and bone marrow morphology
   - Cytogenetics/FISH
   - [redacted]
b. CTL019 cell characterization: Must be done on both peripheral blood and bone marrow, depending on availability of specimens:
   - PK by q-PCR and flow cytometry
   - Immunophenotyping by flow cytometry
c. Immunogenicity (humoral & cellular)
d. Bone Marrow Aspirate: [redacted] If bone marrow aspirate is not available, this analysis can be performed on peripheral blood if tumor cells are present in the peripheral blood at relapse.
e. Physical Examination (including extramedullary disease assessment)

In the event of relapse due to extramedullary disease only, the patient may still be followed per the treatment and primary follow-up phase visit schedule until the institution of systemic antineoplastic therapy.

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. delayed 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 discontinue from the Treatment and Primary Follow-Up phase at Month 10, the first visit in the Secondary Follow-Up Phase will be Month 12.

[redacted]

During the secondary follow-up phase, patients may be monitored remotely by their health care provider or at the investigational site. Patients will undergo one or more of the following at each visit according to Table 7-2: Blood collection for hematology, CTL019 transgene persistence, flow cytometry (B and T cells) and RCL by VSV-G qPCR. If RCL testing is negative through Month 12, all samples taken after Month 12 will be stored for potential future testing. In addition, patients will undergo a physical exam [including height, weight and Tanner staging (only for patients < 18 years old)]. If a patient still in remission cannot attend a regularly scheduled visit during the secondary follow-up, the investigator should attempt to determine relapse status and if the patient receives additional antineoplastic therapies at a minimum.

Adverse events and prior/concomitant medications will be maintained and assessed by the investigational site including emergence of new clinical conditions (see Section 7.1.4.1) and mutagenic agents (cytotoxic drugs, radiation therapy, antineoplastic therapy, and stem cell transplant). If patient is monitored remotely, the investigator will request this information from the patient's health care provider.

Any pregnancies will be reported. Serum or urine pregnancy test will be done for WOCBP until contraception is no longer required (see exclusion criteria #20). A serum pregnancy test will be done for all WOCBP at M60/EOT (Month 60/End of Trial) visit.Efficacy will be assessed in patients who are still in remission until relapse. For these patients, relapse status will be assessed at each visit per Table 7-2 and recorded in the clinical database.

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, is required. If a patient misses an annual scheduled visit where survival status is required, or if the time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact with the patient or correspondence with local health care provider.

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

7.1.4.1 Adverse event and concomitant medication reporting during Secondary Follow-Up Phase

In order to monitor delayed adverse events per Health Authority guidance, selected adverse events/serious adverse events and concomitant medications will be recorded in the clinical database upon investigator knowledge as follows:

Adverse Events/Serious Adverse Events

- 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 and the investigator assess a reasonable relationship to CTL019 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

[redacted]

- New malignancy, other than primary malignancy
- Progressive multifocal leukoencephalopathy (PML)
- Hepatitis B reactivation

Concomitant Medications

- Intravenous Immunoglobulin
- For all patients who are in remission, the first antineoplastic therapy administered (first therapy including conditioning for cell therapy (CAR, SCT) plus cell therapy (CAR, SCT) should be reported.
- Data to support adverse events may be requested.

Please refer to Appendix 4: CTL019 Modified Data Reporting – Secondary Follow Up Phase for reporting.

7.1.4.1.1 Serious adverse event definition

Serious adverse event (SAE) in the Secondary Follow Up phase 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
- 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

[redacted]

7.1.4.2 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.
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

The survival phase intent is to collect survival data on patients that have completed the study. For all patients who complete the primary follow-up phase through 5 years, or complete the secondary follow-up phase through 5 years, additional follow-up will be made to determine survival every 3 months until end of study as defined in Section 4.2, or the patient is enrolled in the long term follow-up study, whichever occurs first. Survival status can be obtained via phone contact with the patient or correspondence with local health care provider. For all patients who are in remission, the first antineoplastic therapy administered (first therapy including conditioning for cell therapy (CAR, SCT) plus cell therapy (CAR, SCT) should be reported.

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

[redacted]

be drawn to evaluate routine safety endpoints, CTL019 vector persistence and RCL. If RCL testing was negative through Month 12, all samples taken after Month 12 will be stored for potential future testing.

7.2 Assessment types

7.2.1 Efficacy assessments

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

An Independent Review Committee (IRC) appointed by Novartis will review data related to disease response assessment according to the Novartis guideline (Appendix 1). The IRC assessment will be used for the primary efficacy analysis. The local investigator assessments will be used for sensitivity analysis for select efficacy endpoints.

Table 7-3 Imaging or disease assessment collection plan – Primary Follow-up Phase

Procedure	Screening / Pre-infusion	Post-infusion Assessments
Bone marrow aspirate and biopsy for morphologic blast cell counts	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Recommended (but not required) at month 3 and 6 and as clinically indicated
Peripheral blood for morphologic blast, neutrophil and platelet cell counts	Mandated	Mandated: Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 (EOT)
Lymph node or other involved tissue aspirate or biopsy	As clinically indicated	As clinically indicated
CSF Assessment/Lumbar puncture for CNS disease	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Additional CSF assessments as clinically indicated
MRD assessments (bone marrow aspirate)	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Recommended (but not required) at month 3 and 6 and as clinically indicated
CNS Brain Imaging (CT/MRI)	As clinically indicated	As clinically indicated
Extramedullary disease assessment (physical exam and CNS symptom assessment)	Mandated	Mandated: Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 (EOT)
Flow Cytometry of peripheral blood (B and T cell, tumor cell, CD19 assessment)	Mandated	Mandated: Days 7, 14, and 21, and Months 1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 (EOT)

[redacted]

7.2.1.1 Physical examination

A targeted physical examination focusing upon sites of extramedullary disease involvement including assessments for hepatomegaly, splenomegaly, skin/gum infiltration, testicular masses and other disease manifestations are required. In addition, the physical examination will also include the assessments of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and the neurological system. 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/assent must be included in the **Medical History** page on the patient's CRF. Significant new findings that begin or worsen after informed consent/assent must be recorded on the Adverse Event page of the patient's CRF. For visits where disease response is assessed (month 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60), assessment results will be recorded on the physical exam disease response CRF page.

7.2.1.2 CNS symptom assessments

Assessment of patient reported symptoms suggestive of leukemic involvement of the CNS will be performed and recorded with each physical examination. Examples of CNS symptoms suggestive of leukemic involvement may include, but are not limited to, severe headache or nausea, meningismus or cognitive impairment, without other apparent etiologies. If clinical signs of CNS leukemia exist, it must be confirmed by CNS imaging (CT or MRI of brain) or other relevant methods (e.g. biopsy, LP, etc.) to define CNS relapse. For visits where disease response is assessed (month 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60), assessment results will be recorded on the CNS disease response CRF page.

7.2.2 Safety and tolerability assessments

Safety will be monitored by physical examination, assessing immunogenicity against CTL019, lab abnormalities as well as collecting adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

Tanner staging for patients less than 18 years of age will be updated semiannually in the treatment and primary follow-up phase, and annually in the secondary follow-up phase. If a patient is classified as Tanner Stage 5 at screening or at any point during the trial, no further Tanner staging will be required for the remainder of the trial. Female patient reproductive status (menstrual status and pregnancy information) will be updated monthly from month 2 through 6, then quarterly through two years, then semiannually thereafter during the primary follow-up phase. Female patient reproductive status will be updated annually in the secondary follow-up phase.

7.2.2.1 Vital signs

Vital signs include temperature, blood pressure, pulse measurements, respiratory rate, and pulse oxygen.

[redacted]

7.2.2.2 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing will be measured via a consistent method at each assessment.

7.2.2.3 Performance status

Table 7-4 Karnofsky/Lansky Performance Scales

Karnofsky Scale (age ≥ 16 years)		**Lansky Scale (age < 16 years)**	
Able to carry on normal activity and to work; no special care needed.		Able to carry on normal activity; no special care is needed	
100	Normal no complaints; no evidence of disease	**100**	Fully active
90	Able to carry on normal activity; minor signs or symptoms of disease	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort; some signs or symptoms of disease	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.		Mild to moderate restriction	
70	Cares for self; unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance, but is able to care for most of his personal needs	**60**	Ambulatory up to 50% of the time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.		Moderate to severe restriction	
40	Disabled; requires special care and assistance	**40**	Able to initiate quiet activities
30	Severely disabled; hospital admission is indicated although death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick; hospital admission necessary; active supportive treatment necessary	**20**	Limited to very passive activity initiated by others (e.g. television)
10	Moribund; fatal processes progressing rapidly	**10**	Completely disabled, not even passive play
0	Dead	**0**	Unresponsive

7.2.2.4 Tanner staging (only for patients < 18 years old)

7.2.2.4.1 Males

Genitalia stages:

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

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

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

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

[redacted]

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

Pubic hair stages:

Stage 1: Pre-adolescent. The velus over the pubesis no further developed than that over the abdominal wall, i.e. no pubic hair.

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

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

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

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

7.2.2.4.2 Females

Breast stages:

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

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

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

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

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

Pubic hair stages:

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

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

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

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

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

[redacted]

7.2.2.5 Laboratory evaluations

Screening and other laboratory assessments will be performed accordingly to Table 7-1 and Table 7-2. Note: Additional assessments should be performed between visits as clinically required to follow AEs or CTL019 expected events and for detailed modified data capture for inpatient/in hospital events, refer to Section 8.1.1. For all laboratory assessments that occur on Day 1, these should be performed prior to CTL019 infusion unless indicated otherwise.

The Investigator will evaluate the clinical significance of each applicable laboratory value outside of the reference range. This decision shall be based upon the nature and degree of the observed abnormality. Values which are considered clinically significant and/or study related to CTL019 will be noted. The Investigator may choose to repeat any abnormal result, in order to rule out laboratory error.

With respect to laboratory assessments listed within this protocol, please refer to the [Laboratory Manual] for further guidance on prioritizing sample acquisition when patient blood volume collection limitations exist.

Table 7-5 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin Concentration (MCHC), MCV (Mean Corpuscular Volume), Platelets, Red blood cells, White blood cells with complete differential (Basophils, Eosinophils, Lymphocytes, Atypical Lymphocytes, Monocytes, Neutrophils, Lymphoblasts, Plasma cells, Prolymphocytes, Myelocytes, Metamyelocytes, and Promyelocytes)
Chemistry	Glucose (fasting or non-fasting), Blood Urea Nitrogen (BUN) or Urea, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Magnesium, Phosphorus, Lactate Dehydrogenase (LDH), Ferritin, C-reactive Protein (CRP) 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	Urine or serum pregnancy test is required at all study office visits from Day 28 to the end of the study as long as contraception is required. Serum testing is required at the timepoints specified in Table 7-1 and Table 7-2.
Viral Serology	Rapid Influenza A & B, Hepatitis C Virus (HCV) RNA qualitative test or antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs), HIV (if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines)
CSF	White Blood Cells, Presence or absence of lymphoblasts, Red Blood cells, Glucose, Protein
Additional assessments	Serum immunoglobulin levels (IgG, IgA, IgM), peripheral blood, donor chimerism (prior allogeneic SCT patients only, or if unknown), bone marrow morphologic blast cell counts, peripheral blood morphologic blast, neutrophil and platelet cell counts, EOI MRD assessment in bone marrow aspirate.

[redacted]

Table 7-6 Central clinical laboratory parameters collection plan

Test Category	Test Name
MRD	MRD flow panel (bone marrow aspirate), B cells, CD19 assessment
Flow cytometry & Blood MRD (treatment and primary follow-up)	B cells, tumor cell immunophenotyping, CD19 assessment
Flow cytometry (secondary follow-up)	Peripheral blood B and T cells
[redacted]	[redacted]
CTL019 assessments (includes T cells)	CTL019 PK by q-PCR and/or flow cytometry (peripheral blood and bone marrow aspirate), CTL019 immunophenotyping by flow cytometry (peripheral blood)
Cytokines	Serum cytokine panel (peripheral blood)
RCL (VSV-G)	VSV-g q-PCR (peripheral blood)
Immunogenicity	Prevalence and Incidence of immunogenicity against CTL019 (peripheral blood and serum)
[redacted]	[redacted]

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

7.2.3 Pharmacokinetics

CTL019 PK and cellular kinetics will be used interchangeably throughout the protocol.

[redacted]

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

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to D-1 Enrollment/Pre-Chemotherapy	3 mL
1	D1 10 min ± 5 min post-infusion	3 mL
1	D4±1d	3 mL
1	D7±1d	3 mL
1	D11 ±1d	3 mL
1	D14±3d	3 mL
1	D21±3d	3 mL
1	D28±4d	3 mL
1	M3±14d	3 mL
1	M6±14d	3 mL
1	M9±14d	3 mL
1	M12±14d	3 mL
1	M18±14d	3 mL
1	M24±14d	3 mL
1	M30±14d	3 mL
1	M36±14d	3 mL
1	M42±14d	3 mL
1	M48±14d	3 mL
1	M54±14d	3 mL
1	M60±14d (EOT)	3 mL
1	Unscheduled (PK samples related to CRS)***	2 mL/collection
1	Unscheduled (PK samples at relapse)****	3 mL
1	Unscheduled (PK samples related to safety events)	3 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.
**All patient sample volumes subject to adjustment for size and patient condition.
*** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS and administration of anti-cytokine therapy, if clinically feasible. Unscheduled PK sample collections related to CRS will cease once PK sample collections related to anti-cytokine therapy commence, if applicable.
**** In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-13)
Note: [redacted]s performed from these same samples (refer to Table 7-17). RCL by VSVg qPCR is performed at the relevant time points using DNA extracted from these samples. If RCL testing was negative through Month 12, all samples taken after Month 12 will be stored for potential future testing.

[redacted]

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

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume
1	W-16 to D-1 Enrollment/Pre-Chemotherapy	2 mL
1	D4±1d	2 mL
1	D7±1d	2 mL
1	D11 ±1d	2 mL
1	D14±3d	2 mL
1	D21±3d	2 mL
1	D28±4d	2 mL
1	M3±14d	2 mL
1	M6±14d	2 mL
1	M9±14d	2 mL
1	M12±14d	2 mL
1	M18±14d	2 mL
1	M24±14d	2 mL
1	M30±14d	2 mL
1	M36±14d	2 mL
1	M42±14d	2 mL
1	M48±14d	2 mL
1	M54±14d	2 mL
1	M60±14d (EOT)	2 mL
1	Unscheduled (PK samples related to CRS)**	2 mL/collection
1	Unscheduled (PK sample at relapse)***	
1	Unscheduled (e.g. related to safety events)	2 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.
***In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-13 and Table 7-14)

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

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to W-12 Screening	2 mL
1	D28±4d	2 mL
1	M3±14d (recommended but not required)	2 mL
1	M6±14d (recommended but not required)	2 mL
1	Unscheduled (PK sample at relapse)	2 mL
1	Unscheduled (e.g. related to safety events)	2 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.
**All patient sample volumes subject to adjustment for size and patient condition.
Note: [redacted] is performed from these same samples; refer to Table 7-17.

[redacted]

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

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to W-12 Screening	2 mL
1	D28±4d	2 mL
1	M3±14d (recommended but not required)	2 mL
1	M6±14d (recommended but not required)	2 mL
1	Unscheduled (PK sample at relapse)	2 mL
1	Unscheduled (e.g. related to safety events, at relapse)	2 mL/collection

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

Table 7-11 CTL019 pharmacokinetics by q-PCR in CSF collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume
1	W-16 to W-12 Screening	4-6 mL
1	D28±4d	4-6 mL
1	Unscheduled	4-6 mL/collection

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

Table 7-12 CTL019 transgene persistence in peripheral blood (for patients in Secondary Follow-up)

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume
1	M3±14d	3 mL
1	M6±14d	3 mL
1	M9±14d	3 mL
1	M12±14d	3 mL
1	M24±14d	3 mL
1	M36±14d	3 mL
1	M48±14d	3 mL
1	M60±14d	3 mL
1	Unscheduled (at relapse)**	3 mL
1	Unscheduled (e.g. related to safety events, at relapse)	3 mL

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.
Note: RCL by VSVg qPCR is performed at the relevant timepoints using DNA extracted from these samples. If RCL testing is negative through Month 12, all samples taken after Month 12 will be stored for potential future testing.
**In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-13 and Table 7-14)

[redacted]

Table 7-13 Immunogenicity serum sample collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to D-1 Enrollment/Pre-Chemotherapy	5 mL
1	D14±3d	5 mL
1	D28±4d	5 mL
1	M3±14d	5 mL
1	M6±14d	5 mL
1	M12±14d	5 mL
1	M24±14d****	5 mL
1	Unscheduled (at relapse)***	5 mL
1	Unscheduled (e.g. related to safety events)	5 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.
**Aliquot obtained from serum cytokine collection; refer to Table 7-17.
*** In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK samples (refer to Table 7-7, Table 7-8, and Table 7-12)
****For patients in Cohort 1 and Cohort 2 as applicable; a corresponding PK sample should be collected at this visit

Table 7-14 Immunogenicity peripheral blood sample collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to D-1 Enrollment/Pre-Chemotherapy	10 mL
1	D14±3d	10 mL
1	D28±4d	10 mL
1	M3±14d	10 mL
1	M6±14d	10 mL
1	M12±14d	10 mL
1	M24±14d****	10 mL
1	Unscheduled (at relapse)***	10 mL
1	Unscheduled (e.g. related to safety events)	10 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified
**All patient sample volumes subject to adjustment for size and patient condition.
Note: Immunophenotyping (peripheral blood) is performed from these same samples; 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, and Table 7-12)
****For patients in Cohort 1 and Cohort 2 as applicable; a corresponding PK sample should be collected at this visit

[redacted]

Table 7-15 Tocilizumab pharmacokinetics (PK), CTL019 PK and sIL6R (PD) in tocilizumab treated patients during CRS

Day/ Scheduled Time Point*/**	Dose Reference ID	Tocilizumab Sample Number	Sample Volume (serum) (PK+PD)	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	--	--	--	--
D1 1 hour ± 15 min post infusion	101	2	5 mL	201	2 mL	601	2 mL
D2 ± 2 hours	101	3	5 mL	202	2 mL	602	2 mL
D3 ± 4 hours	101	4	5 mL	203	2 mL	603	2 mL
D7 ± 1d	101	5	5 mL	204	2 mL	604	2 mL
D1 (pre-dose; second infusion)	101	6	5 mL	205	2 mL	605	2 mL
D1(5-15 minutes post second infusion)	102	7	5 mL	--	--	--	--
D2 ± 2 hours from second infusion	102	8	5 mL	206	2 mL	606	2 mL
D3 ± 4 hours	102	9	5 mL	207	2 mL	607	2 mL
D7 ± 1d	102	10	5 mL	208	2 mL	608	2 mL
D1 (5-15 minutes pre-dose; additional infusion)	102	11	5 mL	209	2 mL	609	2 mL
D1 (5- 15 minutes post additional infusion	103	12	5 mL	--	--	--	--
D2 ± 2 hours	103	13	5 mL	210	2 mL	610	2 mL
D3 ± 4 hours	103	14	5 mL	211	2 mL	611	2 mL
D7 ± 1d	103	15	5 mL	212	2 mL	612	2 mL
Additional ***	104, 105	16, 17, 18, 19, 20	5 mL	213, 214, 215, 216	2 mL	613, 614, 615, 616	2 mL

*All measurement times are relative to tocilizumab infusion 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 of tocilizumab, if clinically feasible. Unscheduled CTL019 PK sample collections related to CRS as specified in Table 7-7, Table 7-8, and Table 7-17 will cease once PK/PD sample collections related to tocilizumab infusion commence, if applicable.
*** Additional PK samples collected in the event more than 2 tocilizumab doses are administered should follow additional PK collection and numbering schedule.

[redacted]

Table 7-16 Siltuximab PK, CTL019 PK and sIL6R (PD) in siltuximab treated patients during CRS

Day/ Scheduled Time Point*/**	Dose Reference ID	Siltuximab Sample Number	Sample Volume (serum) (PK+PD)	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 siltuximab 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 of siltuximab, if clinically feasible. Unscheduled CTL019 PK sample collections related to CRS as specified in Table 7-7, Table 7-8, and Table 7-17 will cease once PK/PD sample collections related to siltuximab administration commence, if applicable.
*** Additional PK samples collected in the event more than 1 siltuximab dose is administered should follow additional PK collection and numbering schedule.

7.2.3.1 Analytical method

The assays to be utilized for various PK/biomarker assessments [redacted] in peripheral blood and other tissues and flow cytometric analysis to detect CTL019 positive cells. Details regarding collection and processing of the samples used in these assays will be provided in the Central Laboratory Manual.

7.2.4 Biomarkers

The plan for biomarker evaluation focuses on characterization of CTL019 cellular pharmacokinetics (see Section 10.5.4), serum cytokines temporally linked to CRS, clonal changes in ALL tumor cells and enumeration of normal B cell levels.

[redacted]

[redacted] These measurements will be used to explore the possible relationships between the relative number of peripheral blood mononuclear cells expressing CTL019 and safety or efficacy outcomes. In parallel, the serum level of inflammatory or immune cytokines will be assessed post-CTL019 administration. These data will be used to retrospectively identify candidate predictive serum markers of CTL019 efficacy and severity of CRS. Finally, the relationship between tumor cell target expression (CD19) and efficacy in addition to the effect of CTL019 on ALL clonal evolution will also be assessed. As part of the [redacted] This assessment will determine if CTL019 eliminates all detectable malignant clones or whether a particular clonal variant is resistant to CTL019 elimination. Additionally, this methodology provides information about the clonal evolution of IGH sequences. In total, [redacted] The effect of CTL019 therapy on normal B cell levels will be measured in peripheral blood and bone marrow aspirate to assess the on-target effect on these CD19 positive cells.

[redacted] Comprehensive DNA sequencing is within scope of these analyses (in accordance with local regulations); at a minimum, targeted sequencing of genes relevant to the CTL019 mechanism of action will be conducted. Finally, [redacted] will be used to explore the correlation between genetics, epigenetics and outcome.

[redacted]

Table 7-17 Biomarker sample collection plan

Day/ Scheduled Time Point*	Sample Volume**
Peripheral blood for serum cytokine analyses	
W-16 to D-1 Enrollment/Pre-Chemotherapy	5 mL
D1 (pre-infusion)	10 mL
D2	5 mL
D4±1d	5 mL
D7±1d	5 mL
D14±3d	5 mL
D21±3d	5 mL
D28±4d	5 mL
M3±14d	5 mL
M6±14d	5 mL
M12±14d	5 mL
Unscheduled (PD samples related to CRS)***	5 mL/collection
*All measurement times are relative to date of CTL019 infusion unless otherwise specified. **All patient sample volumes subject to adjustment for size and patient condition. *** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS and should be consistent with timing of unscheduled PK in Table 7-15 and Table 7-16, if clinically feasible. Please note that results of cytokine analyses are NOT to be used for clinical management decisions of CRS. Unscheduled PK/PD sample collections related to CRS will cease once PK/PD sample collections related to anti-cytokine therapy as specified in Table 7-15 and Table 7-16 commence, if applicable.	
[redacted]	
W-16 to D-1 Enrollment/Pre-Chemotherapy	3 mL
D28±4d	3 mL
M3±14d	3 mL
M6±14d	3 mL
M12±14d	3 mL
*All measurement times are relative to date of CTL019 infusion unless otherwise specified. *Aliquot obtained from CTL019 peripheral blood q-PCR sample as specified in Table 7-7.	
[redacted]	
W-16 to W-12 Screening	2 mL
D28±4d	2 mL
M3±14d (recommended but not required)	2 mL
M6±14d (recommended but not required)	2 mL
*All measurement times are relative to date of CTL019 infusion unless otherwise specified. *Aliquot obtained from CTL019 bone marrow q-PCR aspirate as specified in Table 7-9.	

[redacted]

Day/ Scheduled Time Point*	Sample Volume**
CTL019 Immunophenotyping (peripheral blood)	
W-16 to D-1 Enrollment/Pre-Chemotherapy	10 mL
D7±1d	10 mL
D14±3d	10 mL
D21±3d	10 mL
D28±4d	10 mL
M3±14d (Primary follow-up only)	10 mL
M6±14d (Primary follow-up only)	10 mL
M9±14d (Primary follow-up only)	10 mL
M12±14d (Primary follow-up only)	10 mL
M24±14d (Primary follow-up only)	10 mL
M36±14d (Primary follow-up only)	10 mL
Unscheduled (related to relapse)	10 mL
*All measurement times are relative to date of CTL019 infusion unless otherwise specified. ** Except for collections at M24 and M36, aliquot obtained from peripheral blood immunogenicity assay as specified in Table 7-14.	
Bone marrow [redacted]	
W-16 to W-12 Screening	2 mL
Unscheduled (e.g. related to relapse)	2 mL
Bone marrow [redacted]	
W-16 to W-12 Screening	4 mL
Unscheduled (e.g. related to relapse)	4 mL

7.2.5 Optional additional exploratory assessments using remaining samples

If the patient agrees, the remaining biomarker and/or PK samples as well as any CTL019 manufactured product that is not infused may be stored for up to 15 years and further analyzed to address scientific questions related to CTL019 or cancer, including research related to improvements or enhancements in the manufacturing process. A decision to perform such additional research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

7.2.6 Resource utilization

Hospitalizations will be evaluated in this study as an exploratory endpoint to characterize the impact of study treatment on this aspect of healthcare resource utilization. In addition, these data may be used to support assessments used to characterize the economic impact of study treatment regimens.

Healthcare resource utilization data regarding hospitalizations should be captured from the day of screening up to Month 2 for the patient as described in Table 7-1.

Hospitalizations as a result of the following reasons are not to be reported:

- 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

[redacted]

- Treatments occurring 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 as described in Section 8.2.1 are not required.

Information related to the length of stay (e.g., dates of admission or discharge), hospital ward facilities used (e.g., emergency department, intensive care unit, general ward, etc.), reasons for hospitalization as associated with the study treatment regimen, disease and/or disease progression, or any other reason will be of interest; and hospital discharge information will be evaluated.

7.2.7 Patient reported outcomes

Two questionnaires will be used in this study to capture patient reported outcomes (PROs): PedsQL and EQ-5D. PedsQL™ will be completed by patients aged 8 and above, and EQ-5D will be completed by patients aged 8 and above. Brief description and administration guidelines for each questionnaire are given in the sections below.

The patient should be given the questionnaire(s) and completed at the scheduled visit before the patient sees the investigator or undergoes other clinical assessments. However, for the enrollment visit where the interaction between the physician and the patient cannot be avoided, questionnaire(s) can be completed before or after seeing the investigator. Under extenuating circumstances where the enrollment (baseline) questionnaire(s) was not completed at the enrollment visit, it must be completed before administration of LD chemotherapy or the CTL019 infusion if LD chemotherapy is not administered. Questionnaires should be completed in the language the respondent is most familiar with. The patient should be given sufficient space and time to complete the questionnaire.

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

Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires.

If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what they think the question means. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child has the option of not answering a question if they truly do not understand the question.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs, including SAEs, before any clinical study assessments. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8.

[redacted]

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

The PedsQL is a generic instrument that is commonly used to measure health related quality of life (HRQL) in children and youth aged 0-25. The instrument is available for different age groups and consist of 23 items covering four dimensions of HRQL: Physical functioning, Emotional functioning, Social functioning, and School functioning. The questionnaire requires approximately 5 to 10 minutes to complete.

In this study the following versions of PedsQL will be administered to patients ages of 8 and above:

- PedsQL™ 4.0 (Adult) for patients aged 18 and above at study entry
- PedsQL™ 4.0 (Teens) for patients between the ages of 13-17 at study entry
- PedsQL™ 4.0 (Children) for patients between the ages of 8-12 at study entry

Children (8-12) and Teens (13-18) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen.

If a child has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the child. Since the PedsQL Young Child questionnaire (for ages 5-7) will not be utilized in this trial, a patient in the 8-12 year old age group with difficulty understanding will therefore not complete a PedsQL questionnaire.

7.2.7.2 EuroQol EQ-5D (EQ-5D)

The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults, however, later studies have demonstrated acceptable performance in adolescents aged 12 to 18 years. A child-friendly version, the EQ5DY, has been developed for use in children aged 8 years and older (Wille et al 2010).

The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression).

Patients rate each of these items from “no problem,” “some problem,” or “extreme problem.” A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the “best possible health state” and 0 represents the “worst possible health state.” Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is “today,” and the questionnaire requires approximately 5 to 10 minutes to complete.

In this study the following versions of EQ-5D will be used:

- EQ-5D for patients aged 13 and above at study entry
- EQ-5D-Y for patients between the ages of 8 and 12 at study entry.

7.2.7.3 Questionnaire administration

Completion of the following questionnaire(s) will be required based on age at study entry:

[redacted]

Age at study entry	PedsQL™ V4 Version	EQ-5D Version
2-4	Not Done	Not Done
5-7	Not Done	Not Done
8-12	PedsQL (Children)	EQ-5D-Y
13-17	PedsQL (Teen)	EQ-5D
18+	PedsQL (Adult)	EQ-5D

Please refer to the Guidelines for administering the PRO questionnaires for further instruction. If a child has difficulty understanding the age-appropriate questionnaire version, the preceding age group version may be administered to the child, if available. If a translated language is not available for the local country language(s) or a patient's native language, questionnaire completion is not required.

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.

Under the circumstance when a patient is simultaneously enrolled in the active phase (up to Day 2) of the Novartis CTL019B2206 leukapheresis (apheresis collection) protocol and this treatment protocol, collection and reporting of adverse events during this overlapping period should follow the CTL019B2206 safety reporting criteria.

[redacted]

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, 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. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria:
    - Require anti-infective treatment OR
    - Lead to significant disability or hospitalization OR
    - Need for 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 (≥ Grade 3) 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 but is collected as a seriousness criteria; 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:

[redacted]

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 and which seriousness criteria have been met.

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.

Progression underlying malignancy with fatal outcome should be reported as SAE irrespective of causality, if it occurs within 30 days post CTL019 infusion. After 30 days, progression of underlying malignancy should be reported as SAE only, if there is at least a possible causal relationship to CTL019. Progression of underlying malignancy without fatal outcome should not be reported as an AE.

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. 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. A 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

[redacted]

response/resolution following intervention. Details can be found in the CRF Completion Guidelines (CCGs).

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 reported as such.

8.1.4 Adverse events of special interest

Adverse events of special interest (AESI) are described in Table 10-3. The current search criteria of AESI are based on limited experience from ongoing clinical studies without an accurate assessment of causality. The search criteria of the AESI may be updated prior to database lock for primary analysis reporting. Based on current clinical experience, AESI typically occur and resolve within 8 weeks of CTL019 infusion in ALL patients.

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

[redacted]

  - 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/assent
  - 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

8.2.2 Reporting

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 if 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 clinical status of the patient that the investigator deems may have a potential impact on the patients during lymphodepletion and CTL019 treatment

Under the circumstance when a patient is simultaneously enrolled in the active phase (up to Day 2) of the Novartis CTL019B2206 leukapheresis (apheresis collection) protocol and this treatment protocol, collection and reporting of serious adverse events during this overlapping period should follow the CTL019B2206 safety reporting criteria.

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.

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. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria:

[redacted]

  - Require anti-infective treatment OR
  - Lead to significant disability or hospitalization OR
  - Need for 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 (≥ 3 Grade) adverse event or condition the investigator believes may have a reasonable relationship to CTL019 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

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 deaths regardless of attribution following lymphodepleting chemotherapy and/or CTL019 infusion and within 30 days of receiving CTL019 infusion
- Deaths attributed to CTL019 occurring 30 days post CTL019 infusion

Any SAEs experienced after the Month 60 (EOT) visit should only be reported to Novartis Chief Medical Office and Patient Safety (CMO&PS) 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.

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. 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 drug 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 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 should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship between CTL019 and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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

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.

8.5 Warnings and precautions

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

8.6 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 at regular intervals the safety data of the patients treated in 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 pediatric hematology/oncologist) and one biostatistician.

[redacted]

There will be an initial meeting with the DMC to have agreement on their roles and responsibilities and the 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 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 outcome.

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.

8.7 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.

8.8 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 remission 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 Appendix 1. Patient management will be based upon local investigator assessments. The designation of remission 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.

9 Data collection and management

9.1 Data confidentiality

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

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information

[redacted]

- The rights of a research patient to revoke their authorization for use of their PHI

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients 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 patient 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.

Prior to entering key sensitive personally identifiable information (patient initials and exact date of birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit patient initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated Contract Research Organization [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/assent form (a 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/assent, 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

[redacted]

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 eCRFs are complete, accurate, and that entry and updates are performed in a timely manner.

The Novartis designated manufacturing facility is responsible for assuring that the manufacturing specific data entered into eCRFs are 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 World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history and adverse events will be coded using the MedDRA terminology.

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.

The Novartis designated manufacturing facility is responsible for assuring that the manufacturing specific data entered into eCRFs are complete, accurate, and that entry and updates are performed in a timely manner.

10 Statistical methods and data analysis

Data from all participating centers will be combined.

Main Cohort

An interim analysis will be performed when the first 50 patients who receive CTL019 have completed 3 months follow-up from study day 1 infusion or discontinued earlier. At the time of this interim analysis, assessment of all endpoints will be based only on patients who receive CTL019 manufactured from US manufacturing facility because there will be no patients treated with CTL019 manufactured from other manufacturing facilities.

The final analysis of the primary endpoint will be performed after all patients infused with CTL019 have completed 3 months follow-up from study day 1 infusion or discontinued earlier. Selected efficacy and safety analysis will be updated annually.

Cohort 1 and Cohort 2

Patients in Cohort 1 will be analyzed separately. At the time of enrollment termination, only 1 patient was enrolled and infused in Cohort 1. Therefore, only listings of this single patient will be presented. No patients were enrolled in Cohort 2.

[redacted]

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.

10.1.1 Screened Set

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

10.1.2 Enrolled Set

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

10.1.3 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned, and have received infusion of CTL019.

10.1.4 Interim Efficacy Analysis Set

At the time of interim analysis, the Interim Efficacy Analysis Set (IEAS) comprises the first 50 patients who receive CTL019 infusion.

10.1.5 Safety Set

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

10.1.6 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the IEAS or FAS (at interim and final analysis respectively) who are compliant with major requirements of the clinical study protocol (CSP).

Major protocol deviations leading to exclusion from the PPS include:

- No diagnosis of ALL at baseline;
- Prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens;
- Missing or incomplete documentation of disease;

In addition, patients who receive a dose less than the minimum target dose of 2×10^6/kg (for patients $\leq$ 50 kg) or 1×10^8 (for patients > 50 kg) CTL019 transduced viable T cells will also be excluded.

The detailed exclusion criteria of PPS will be determined prior to primary analysis.

[redacted]

10.1.7 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of IEAS or FAS (at time of interim or final analysis respectively) who have at least one sample providing evaluable pharmacokinetic (PK) data. The PAS will be used for summaries (tables and figures) and listings of PK data.

Note that patients will 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.

10.2 Patient demographics/other baseline characteristics

The following analyses will be performed in Main Cohort. Only listings (i.e., demographic and other baseline data, prior disease history, etc.) will be presented in Cohort 1. No patients were enrolled in Cohort 2.

Demographic and other baseline data will be listed by patient and/or summarized descriptively for the FAS as well as for IEAS. 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 the prior allogeneic SCT status (with prior SCT, without prior SCT).

Patients will also be classified by their prior response status into:

- Primary refractory: If patient never had a morphologic complete remission (CR) prior to the study
- Relapsed disease: If patient had a CR from other therapy and relapsed prior to the study

10.3 Treatments (study treatment, concomitant therapies, compliance)

The following analyses will be performed in Main Cohort. Only listings (i.e., total cells infused, total CTL019 transduced viable T cells, prior or concomitant medications, etc.) will be presented in Cohort 1.

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

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

[redacted]

10.4 Primary objective

For the Main cohort and Cohort 1 (enrollment into Cohort 1 has been terminated as of 15-Jun-2020), the primary objective of the study is to evaluate the efficacy of CTL019 therapy as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment in the FAS population.

For Cohort 2 (enrollment into Cohort 2 has been terminated as of 15-Jun-2020), the primary objective is to assess the safety and feasibility to administering CTL019 within 6 months post allo-HSCT. In addition, sensitivity analysis will be performed using the local investigator response assessments instead of the IRC assessment.

10.4.1 Variable

The primary efficacy endpoint for Main cohort and Cohort 1 is the ORR as determined by IRC assessment during the 3 months after CTL019 administration. The ORR is defined as the proportion of patients with a best overall disease response of CR or CRi, where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until the start of new anticancer therapy. Best response will be assigned according to the following order:

- CR
- CRi
- No response (NR)
- Unknown

[redacted]

Table 10-1 Definition of CR, CRi and relapse at a given evaluation time

Response category	Definition
Complete remission (CR)	All the following criteria are met: **Bone marrow** • < 5% blasts **Peripheral blood** • Neutrophils > 1.0 x 10^9/L, and • Platelets > 100 x 10^9/L, and • Circulating blasts < 1% **Extramedullary disease** • No evidence of extramedullary disease (by physical exam and CNS symptom assessment) **Transfusion independency** • No platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	All criteria for CR as defined above are met, except that the following exist: • Neutrophils ≤ 1.0 x 10^9/L, and/or • Platelets ≤ 100 x 10^9/L, and/or • Platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Relapsed Disease	Only in patients who obtained a CR or CRi: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi

A full response evaluation, including assessments of peripheral blood, bone marrow, CNS symptoms, physical exam, and CSF assessment by LP, is required at the first time a CR or CRi is demonstrated. Bone marrow biopsy/aspirate and CSF assessment by LP are required 1 month (Day 28) after infusion. If the patient is not in CR/CRi at Month 1, then a bone marrow biopsy/aspirate and CSF assessment by LP are also required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) to establish that a patient has achieved CR/CRi for the first time. Additional bone marrow biopsies/aspirates and CSF assessments by LP are not required after initial establishment of CR or CRi unless clinically indicated (recommended but not required at months 3 and 6).

Complete remissions in patients with ALL have been observed to take place within 1 month after infusion with CTL019. The onset of complete remissions are rapid and dramatic, and patients quickly regain a normal performance status. ALL relapse in the bone marrow is rapidly followed by signs or symptoms of disease recurrence as well as abnormalities in the peripheral blood.

Therefore, following initial achievement of CR/CRi, patients will be considered to have maintained a clinical CR/CRi if the patient has no evidence of extramedullary disease (by physical exam and CNS symptom assessment) and circulating blasts in peripheral blood are <1%. In order for the best ORR to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment

[redacted]

(physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. Please note, if additional assessments of bone marrow and/or CSF are performed in the same evaluation, they will also need to show remission status.

See Appendix 1 for details of disease response criteria.

The primary safety endpoints for Cohort 2 are adverse events and laboratory abnormalities as defined in Sections 10.5.3.2 and Section 10.5.3.3.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed in Main Cohort by testing whether the ORR within 3 months is less than or equal to 20% against the alternative hypothesis that ORR within 3 months 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 primary efficacy endpoint, ORR within 3 months, will be analyzed at the interim look and final look of a group sequential design. The ORR will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets as implemented in East 5.4 (Lan and DeMets, 1983). The study will be considered successful if the lower bound of the 2-sided 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.

The primary efficacy endpoint, ORR will be analyzed based on the data observed in the IEAS and FAS at interim and final analysis, respectively. Hypothesis testing of primary endpoint will only be performed for patients in Main cohort.

Only the listing of ORR per IRC and local investigator will be presented in Cohort 1.

10.4.3 Handling of missing values/censoring/discontinuations

Patients in the study who are of unknown clinical response will be treated as non-responders. See also the Novartis guideline for efficacy evaluation in ALL (Appendix 1) for more details.

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

10.4.4 Supportive analyses

The analysis of the primary efficacy endpoint for Main cohort will be performed among all patients in the PPS using the same methodology as outlined at interim and final analysis, respectively.

The analysis of primary efficacy endpoint for Main cohort will also be performed among all patients in the Enrolled Set who have either discontinued prior to CTL019 infusion or have received CTL019 infusion.

In addition, the analysis of the primary efficacy endpoint for Main cohort will also be performed using all patients who satisfy all clinical eligibility criteria and have either discontinued prior to CTL019 infusion or have received CTL019 infusion.

[redacted]

10.4.4.1 Subgroup analysis

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

- Age: <10 years, ≥10 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: White, Asian, Other
- Ethnicity: Hispanic or Latino, Other
- Prior response status: Primary refractory, Chemorefractory, Relapsed disease
- Prior SCT therapy: Yes, No
- Eligibility for SCT: Eligible for SCT, ineligible for SCT
- Baseline bone marrow tumor burden: Low (defined as either morphologic or MRD result is <50% and neither is ≥50%), High (defined as either morphologic or MRD result is ≥50%)
- Baseline extramedullary disease presence: Yes, No
- Philadelphia chromosome/BCR-ABL: Positive, Negative
- Mixed-Lineage Leukemia (MLL) rearrangement: Yes, No
- Hypoploidy: Yes, No
- *BCR-ABL1-like*: Yes, No
- Complex Karyotypes (≥5 unrelated abnormalities): Yes, No
- Down syndrome: Yes, No

The rationale for performing subgroup analyses are as follows:

- Age, gender, race and ethnicity are demographic factors that are typically requested by health authorities to assess internal consistency of the study results.
- Prior response status is a key prognosis factor due to potentially higher rates of treatment related morbidity in patients who have relapsed following allogeneic SCT.
- Baseline bone marrow tumor burden and extramedullary disease presence are important indicators of overall disease burden, which is a potential predictive factor.
- BCR-ABL, MLL rearrangement, hypoploidy, *BCR-ABL1-like* gene signatures and complex karyotype (≥ 5 unrelated abnormalities) are high risk factors for ALL. Patients with these high risk factors have poorer diagnosis (Harrison 2010; van der Veer 2013). In case there are very few patients with these high risk mutations individually, analysis may be performed for patients with any of these high risk mutations versus those who do not.
- Patients with Down Syndrome is known to have increased ALL treatment related morbidity and mortality rates. Because of increased risk, stem cell transplant is often not recommended in this population. Therefore, the experience with CTL019 in this rare population may offer an unmet medical need.

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.

In addition, Japanese patients will be analyzed separately in descriptive manner.

[redacted]

10.5 Secondary objectives

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

10.5.1 Key secondary objective(s)

Hypothesis testing of key secondary end-points will only be performed for patients in Main cohort.

10.5.1.1 ORR within 3 months in all patients infused with CTL019 from US manufacturing facility

The first key secondary objective of the study is to evaluate the efficacy of CTL019 therapy from US manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration by IRC assessment.

The hypothesis testing will be performed to test whether the ORR within 3 months is less than or equal to 20% against the alternative hypothesis that ORR is greater than 20%.

This hypothesis testing will only be performed when the primary objective is met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5% level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 20%, so that the null hypothesis above can be rejected.

10.5.1.2 Remission with MRD negative bone marrow in patients infused with CTL019 from all manufacturing facilities

The second key secondary objective of the study is to evaluate the percentage of patients who receive CTL019 from all manufacturing facilities and achieve a BOR of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry during the 3 months after CTL019 administration. The main analysis of this key secondary objective will be performed among all patients in the IEAS or FAS population, at the time of interim and final analysis respectively. See Appendix 1 for details of determination of MRD negativity.

This key secondary efficacy analysis will be performed by testing whether the percentage of MRD negative responder among all patients who received CTL019 infusion from all manufacturing facilities in IEAS or FAS as defined above is less than or equal to 15% against the alternative hypothesis that it is greater than 15% at overall one-sided 2.5% level of significance, i.e.,

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

This hypothesis testing will only be performed when both the primary objective and the first key secondary endpoint are met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be

[redacted]

controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5 % level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 15%, so that the null hypothesis above can be rejected.

The key secondary endpoint will also be summarized among who achieve a BOR of CR or CRi during the 3 months after CTL019 administration.

Additional analysis will be done using the qPCR MRD analysis instead of flow cytometry (exploratory only).

10.5.1.3 Remission with MRD negative bone marrow in patients infused with CTL019 from US manufacturing facility

The third key secondary objective of the study is to evaluate the percentage of patients who achieve a BOR of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry during the 3 months after CTL019 administration among all patients who receive CTL019 from US manufacturing facility.

The hypothesis testing will be performed to test whether the above rate is less than or equal to 15% against the alternative hypothesis that it is greater than 15%.

This hypothesis testing will only be performed when both the primary objective and the first two secondary endpoints are met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5% level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 15%, so that the null hypothesis above can be rejected.

10.5.2 Other secondary efficacy objectives

The secondary efficacy objectives are outlined as follows in the order of importance.

Additional analyses will be performed to further assess the efficacy of CTL019 treatment by combining data collected in this protocol together with the 15 year long term follow-up protocol, if appropriate.

10.5.2.1 Percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment

The percentage of patients who achieve CR or CRi at Month 6 without SCT (post CTL019 infusion) between CTL019 infusion and Month 6 response assessment, among all patients in the FAS, will be summarized along with exact 95% Confidence Interval (CI). In addition, the percentage among patients who achieved CR or CRi will also be summarized. The time of

[redacted]

proceeding to SCT is defined as the time of commencing the conditioning regimen as required for hematopoietic SCT. This definition applies to all analyses.

This analysis will be conducted when all patients have completed 6 months post CTL019 infusion or have discontinued earlier.

10.5.2.2 Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment

The percentage of patients who achieve CR or CRi and then proceed to SCT while in remission by the time of Month 6, among all patients in the FAS, will be summarized along with exact 95% CI. In addition, the percentage will also be summarized among all patients who achieved CR or CRi.

This analysis will be conducted when all patients have completed 6 months post CTL019 infusion or have discontinued earlier.

All patients that proceed to SCT post CTL019 infusion will be listed.

10.5.2.3 Duration of remission (DOR)

Duration of remission (DOR) is defined as the duration from the date when the response criteria of CR or CRi is first met to the date of relapse or death due to underlying cancer.

In case a patient does not have relapse or death due to ALL 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 SCT)
- Event after at least two missing scheduled disease assessments

In addition, death due to reason other than ALL will be considered as a competing risk event to other events of interest (relapse or death due to ALL).

As SCT is an important treatment option in responding patients, it is appropriate to consider the date of SCT as censoring date, instead of censoring at the last tumor assessment date. However, censoring due to SCT will overestimate the rate of relapse and therefore may be considered inappropriate for the main analysis when a substantial number of patients choose to receive SCT (CHMP 2010). If a patient received SCT after a CR or CRi, relapse or survival status after SCT will be recorded on the corresponding follow-up eCRFs, although data on individual disease response components (e.g. bone marrow) will not be collected. In such cases, the date of relapse or death (if due to the underlying cancer) after SCT will be used for the calculation of DOR as a sensitivity analysis.

Additional sensitivity analysis will be performed by censoring death due to reason other than ALL instead of considering it as the competing risk event to other events of interest (relapse or death due to ALL).

[redacted]

The proposed analyses for DOR are summarized in Table 10-2 below. Method 1 will be considered as the main analysis for DOR. Additional analyses may be considered.

Table 10-2 Analyses of duration of response (DOR)

	Death due to reason other than ALL	SCT after remission
Method 1	Competing risk analysis	Censor at time of SCT
Method 2	Censor at last adequate tumor assessment	Censor at time of SCT
Method 3	Competing risk analysis	Ignore SCT
Method 4	Censor at last adequate tumor assessment	Ignore SCT

DOR will be assessed only in patients with the best overall response of CR or CRi. The estimated percentage of relapsed patients (at 6 months, 12 months, etc.) will be presented with 95% confidence intervals using the cumulative incidence function (CIF) or the Kaplan-Meier (KM) method.

For Method 1 and Method 3, the CIF is used to estimate the probability of the event of interest in the presence of the competing risks (Kim 2007).

For Method 2 and Method 4, the distribution function of DOR will be estimated using the KM method. The median DOR along with 95% confidence intervals will be presented if appropriate.

Method 1 and Method 3 will be conducted only if there are any patients who respond to CTL019 but experience the event of death due to reasons other than ALL.

If a considerable number of patients receive SCT while in remission after CTL019 infusion, then exploratory analyses may be performed on patients who achieve CR/CRi after CTL019 infusion to assess the effect of SCT on DOR. Baseline disease characteristics and post-baseline factors (e.g. time to CR/CRi, minimal residual disease) that may be correlated with the decision to receive SCT and with DOR will be identified. A Cox model with SCT as a time dependent covariate and potential confounding factors as additional covariates may then be explored in patients who achieve CR/CRi after CTL019 infusion. The hazard ratio (SCT v/s No SCT after CR/CRi) estimate along with its 95% confidence interval will be provided. Additional exploratory analyses may be considered to account for the confounding factors.

10.5.2.4 Relapse free survival (RFS)

Relapse free survival (RFS) is measured by the time from achievement of CR or CRi whatever occurs first to relapse or death due to any cause during CR or CRi.

In case a patient does not have relapse or death due to any cause prior to data cutoff, RFS 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 SCT)
- Event after at least two missing scheduled disease assessment

[redacted]

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

RFS will be assessed only in patients with the best overall response of CR or CRi. The distribution function of RFS will be estimated using the KM method. The median RFS along with 95% confidence intervals will be presented if appropriate.

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

In case of treatment failure, the event date will be set to study Day 1 (CHMP 2010).

In case a patient does not have relapse, death due to any cause or treatment failure (e.g. discontinuation as a result of withdrawal of consent, lost to follow-up, protocol violation or administrative problems) prior to data cutoff, EFS is censored at the last adequate response assessment date on or prior to the earliest censoring event (except for SCT). The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Event after at least two missing scheduled disease assessment

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

EFS will be assessed in all patients in IEAS and FAS. 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.

10.5.2.6 Overall survival (OS)

Overall survival (OS) is the time from date of first CTL019 infusion to the date of death due to any reason.

[redacted]

In case a patient is alive at the date of last contact on or before data cutoff, OS is censored at the date of last contact. No censoring will be done in case of SCT. Thus, patients should be followed-up for survival also in case of SCT.

OS will be assessed in all patients in IEAS and FAS. The distribution function of OS will be estimated using the Kaplan Meier (KM) method. The median OS along with 95% confidence intervals will be presented if appropriate.

10.5.2.7 Patient Reported Outcome

Patient Reported Outcome (PRO), such as scores of health-related quality of life questionnaires PedsQL and EQ-5D will be assessed. PedsQL™ will be completed by patients aged 8 and above, and EQ-5D will be completed by patients aged 8 and above. Descriptive statistics (e.g. mean, median, and frequency) and change from baseline of the summary scores for each post baseline time-point/window of assessment will be provided based on all available data at the time of final analysis. FAS will be used for all analysis.

10.5.2.8 Response at Day 28 +/- 4 days

Proportion of patients attaining CR or CRi at Day 28 +/- 4 days post CTL019 infusion, in the same analysis set as for the primary endpoint, will be summarized along with exact 95 % Confidence Interval (CI).

10.5.2.9 Impact of baseline tumor burden on response

Best overall response will be summarized by baseline tumor burden (MRD, extramedullary disease, etc).

10.5.2.10 Quality of response using MRD disease assessments

The quality of response using MRD disease assessments before treatment, and at day 28 +/- 4 days after treatment using central assessment by flow cytometry and before SCT by local assessment (flow or PCR) will be summarized descriptively.

Both quantitative MRD result and qualitative results (positive/negative) will be summarized if available.

10.5.2.11 Efficacy, safety and CTL019 PK in patients infused with CTL019 manufactured by Fraunhofer Institute

The ORR and MRD negative remission rate will be summarized with 95% exact confidence intervals for patients infused with CTL019 manufactured by Fraunhofer Institute.

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 performed on the Safety Set.

The CTL019 PK parameters for CTL019 transgene levels as measured by q-PCR will also be summarized. The CTL019 PK parameters as measured by flow cytometry (exploratory only) will also be summarized, as appropriate.

[redacted]

10.5.2.12 Efficacy in Cohort 1 and Cohort 2

DOR, EFS and OS will be listed in Cohort 1. No patients were enrolled in Cohort 2.

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

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

- pre-infusion period: from day of patient's informed consent/assent to the day before 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.

Summary tables for adverse events have to include only AEs that started or worsened during the post-infusion period, i.e. the **treatment-emergent** AEs. However, all safety data (including those from the pre-infusion period) will be listed and those collected during the pre-infusion period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by 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 reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Adverse events of special interest (AESI) search criteria are updated on a regular basis at the CTL019 program level. The most recent version of the AESI search criteria form will be used for the reporting activity. The current AESI search criteria are described in Table 10-3 below. AESI that occur within 8 weeks of the CTL019 infusion will be summarized by group term and preferred term.

[redacted]

Table 10-3 Adverse events of special interest (AESI) search criteria

AESI group term	MedDRA term or other search criteria	Type
Cytokine Release Syndrome	Cytokine Release Syndrome	PT
	Cytokine storm	PT
	Shock	PT
	Macrophage Activation	PT
	Histiocytosis haematophagic	PT
Tumor Lysis Syndrome	Tumor Lysis Syndrome	SMQ
Febrile neutropenia	Neutropenic infection	PT
	Neutropenic sepsis	PT
	Febrile neutropenia	PT
Infection	Infections and infestations	SOC
Transient neuropsychiatric events	Noninfectious encephalopathy/ delirium	SMQ
Hematopoietic cytopenias not resolved by day 28	Haematopoietic cytopenias	SMQ
	Lab abnormalities which do not resolve at least 28 days post CTL019 infusion	Lab

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, biochemistry and urinary 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)

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

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. Cellular immunogenicity assessment will include percentage of CD4+ and CD8+ T cells specific for CTL019 as an exploratory analysis and reported as appropriate.

[redacted]

10.5.3.5 Derivation of a score to predict cytokine release syndrome

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

10.5.3.6 Soluble immune factors

Soluble immune and inflammatory cytokines (e.g. IL-10, interferon gamma, IL-6, IL-6 receptor, CRP, and ferritin) will be listed and summarized by patient and time point. Baseline and absolute and relative change (percent and or fold change) from baseline will be calculated for each treatment group and time point and summarized using sample size, mean, standard deviation, median, minimum and maximum. If both the baseline and post baseline values are below LLOQ, absolute, percent and fold change from baseline will not be imputed and reported as missing. Baseline levels may also be summarized by clinical response status and severity of CRS and potentially graphed using strip plots. In addition, the maximum change from baseline measure for each cytokine may also be graphed against clinical response status and severity of CRS response using strip plots. Patient level and averaged cytokine measures and percent change from baseline may be displayed using longitudinal plots.

The general principles of analyzing biomarker data as outlined in Section 10.6.1 should also apply.

10.5.3.7 B-cell and T-cell level

The levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion will be described.

Malignant and normal B cell populations will be listed and summarized by patient and time point. Baseline and absolute and relative change (percent change) from baseline will be calculated and summarized using sample size, mean, standard deviation, median, minimum and maximum. Baseline and change from baseline to minimum cell number may also be summarized by response status and potentially graphed using strip plots. Patient level and averaged cell counts and percent change from baseline may be displayed using longitudinal plots.

It is anticipated that all patients who achieve complete remission will exhibit B-cell aplasia. Timing of B-cell recovery will be summarized.

CD8 and CD4 positive T cells will be listed and summarized by time point. Data may also be summarized by response status and potentially graphed using strip plots. Patient level and average longitudinal plots of the cell counts and percent changes from baseline may be generated.

The general principles of analyzing biomarker data as outlined in Section 10.6.1 should also apply.

For abnormal T cell or B cell results, associated safety events such as infections and use of associated therapies (i.e. antibiotics, immunoglobulin replacement) will be investigated using patient listings

[redacted]

10.5.3.8 Other safety data

Vital signs will be collected as clinically needed. Findings supportive of GVHD will be listed for patients who have received prior allogeneic SCT. All safety data will be listed.

10.5.3.9 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: <10 years, ≥10 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: White, Asian, Other
- Ethnicity: Hispanic or Latino, Other
- Prior response status: Primary refractory, Chemorefractory, Relapsed disease
- Prior SCT therapy: Yes, No
- Down syndrome: Yes, No

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

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

10.5.3.10 Safety in Cohort 1 and Cohort 2

All safety data (i.e., adverse events, AESI, key laboratory parameters, immunogenicity data, etc.) will be listed for Cohort 1. .

10.5.4 Pharmacokinetics

The following analyses will be performed for Main Cohort only. Only listings (i.e., PK parameters, CTL019 transgene level) will be presented for Cohort 1.

CTL019 concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed, and summarized by time point as assessed by the following (see Section 10.6.1):

- CTL019 transgene levels as measured by q-PCR,
- CTL019 transduced cells measured by flow cytometry of CD3-positive,
- CTL019 transduced cells measured by flow cytometry of CD3-positive/ CD4-positive and CD3-positive/CD8-positive CTL019 transduced cells. (exploratory only)

The PK parameters listed in Table 10-4 along with other relevant PK parameters will be estimated from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix® (Pharsight, Mountain View, CA). The non-quantifiable concentrations will be imputed to zero for PK concentration summaries, and 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.

[redacted]

Table 10-4 Noncompartmental pharmacokinetic parameters

Parameter	Definition
AUC 0 - Tmax	The AUC from time zero to T_{max} in peripheral blood (% or copies/µg x days)
AUC Tmax - 28d and M3	The AUC from time Tmax to day 28 and M3 or other disease assessment days, in peripheral blood (% or copies/µg x days)
AUC 0 - 28d and M3	The AUC from time zero to day 28 and M3 or other disease assessment days, in peripheral blood (% or copies/µg x days)
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)

Descriptive statistics of PK parameters will be summarized by mean, standard deviation, coefficient of variation, min and max. When a geometric mean will be presented, it will be stated as such. A range of values will be presented for selected variables. Since T_{max} is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

The relationship between anti-cytokine treatment, use of steroids, occurrence of immunogenicity or other relevant covariates and PK will be explored. Population or mechanistic PK/PD models may also be generated for ALL patients. For patients whose tocilizumab PK data were collected during CRS, the tocilizumab concentrations will be summarized by time points, relative to time of tocilizumab dose as appropriate and supported by data.

10.6 Exploratory objectives

10.6.1 Biomarkers

As a project standard, Novartis Oncology Biostatistics and Data Management will analyze only biomarkers collected in the clinical database. For exploratory markers, since the studies are not adequately powered to assess specific biomarker–related hypotheses, the goal of these exploratory statistical analyses should be considered as the generation of new scientific hypotheses or observing new trends. These hypotheses may be compared with results found in literature as well as verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is usually planned for exploratory analyses. Furthermore, additional post hoc exploratory assessments are expected and may be performed in Main Cohort.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood due to either practical or strategic reasons (e.g. issues related to the quality of the sample). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

[redacted]

10.6.1.1 Biomarker Data Analysis Set

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

10.6.1.2 Data handling

Serum cytokine data are generally log normally distributed. A Log2 transformation of the data is typically required for normalization prior to performing any statistical assessments. Values below the lower limit of quantitation (which may be reported with the label Lower Limit of Quantification [LLOQ]) or have a numerical value below the assay's lower limit of quantification) will be imputed / replaced as 0.5×LLOQ, which will be specified by the performing lab and is assay and analyte specific. In some cases a value, although below LLOQ, is reported, this value should not be used and the data should be imputed as 0.5×LLOQ.

10.6.1.3 Basic tables, listings and figures

For Main Cohort, the ALL [redacted] as measured by [redacted] will be listed per patient and percent change from baseline will be summarized using sample size, mean, standard deviation, median, minimum and maximum. Patient level absolute and relative changes may be displayed using longitudinal plots. Additional analyses [redacted] that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the RAP or in a stand-alone analysis plan document, as appropriate.

10.6.2 CTL019 product characteristics

Selected clinical outcomes will be summarized descriptively by CTL019 product characteristics [redacted] for the Main Cohort.

10.6.3 Cytokine release syndrome

To explore the relationship between CRS and other endpoints, the goal of this statistical analysis should be considered as the generation of new scientific hypotheses and observing new trends, since the studies are not adequately powered to propose a scoring system. For Main Cohort, information regarding the severity of cytokine release syndrome, and response to anti-cytokine therapy, if any, will be listed and summarized. The summarization is descriptive only to be in line with its exploratory nature. Summary by initial tumor burden, clinical tumor response status, and PK/PD parameters may be explored.

10.6.4 Healthcare resource utilization

Data relating to resource utilization (described in Section 7.2.6) will be used to support health economic evaluations.

[redacted]

Number of CTL019 inpatients and outpatients infusions will be summarized in Main Cohort. Descriptive statistics of hospitalizations, including the total and average number and duration of hospitalizations, will be provided in Main Cohort.

Details of data analysis will be specified in the analysis plan as appropriate.

10.7 Interim analysis for Main Cohort

10.7.1 Interim analysis for the primary endpoint

An interim analysis is planned when the first 50 patients infused have completed 3 months from study day 1 infusion or discontinued earlier. The interim analysis will be performed by testing the null hypothesis of ORR within 3 months being less than or equal to 20% against the alternative hypothesis of ORR within 3 months being greater than 20% at overall one-sided 2.5% level of significance.

The study will not be stopped for outstanding efficacy at the interim analysis regardless of the interim result.

An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in East 5.4, will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983). Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 76 patients (i.e. 50/76=65.8% information fraction), the lower bound of the 2-sided 98.9% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 19/50 = 38% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.4% exact CI will be used at final analysis correspondingly. As a result, an ORR of 23/76 = 30% will be needed to claim success at final analysis.

The efficacy boundary at the final analysis will be based on the actual number of patients and the alpha already spent at the interim analysis. If the number of patients in the final analysis deviates from the expected number of patients, the final analysis criteria will be determined so that the overall significance level across all analyses is maintained at one-sided 0.025.

10.7.2 Interim analysis for the key secondary endpoints

If the primary endpoint is met at the interim analysis, the key secondary endpoints will also be assessed following hierarchical sequence using an α-spending function according to Lan-DeMets (O'Brien-Fleming).

10.7.2.1 ORR within 3 months in all patients infused with CTL019 from US manufacturing facility

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 66 patients (i.e. 50/66=75.8% information fraction), the lower bound of the 2-sided 98.0% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 18/50 = 36% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.6% exact CI will be used at final analysis correspondingly. As a result, an ORR of 21/66 = 32% will be needed to claim success at final analysis.

[redacted]

10.7.2.2 Remission with MRD negative bone marrow in patients infused with CTL019 from all manufacturing facilities

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 76 patients (i.e. 50/76=65.8% information fraction), the lower bound of the 2-sided 98.9% exact CI will need to be greater than 15% to declare statistical significance. As a result, a MRD negative rate of 15/50 = 30% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.4% exact CI will be used at final analysis correspondingly. As a result, an ORR of 19/76 = 25% will be needed to claim success at final analysis.

10.7.2.3 Remission with MRD negative bone marrow in patients infused with CTL019 from US manufacturing facility

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 66 patients (i.e. 50/66=75.8% information fraction), the lower bound of the 2-sided 98.0% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 15/50 = 30% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.6% exact CI will be used at final analysis correspondingly. As a result, an ORR of 17/66 = 26% will be needed to claim success at final analysis.

10.8 Sample size calculation

Main Cohort

In a previous study of clofarabine in patients with r/r B-cell ALL who have had 2 or more prior regimens, the reported ORR was 20% (95% CI [10%, 34%], Jeha et al (2006)). Hence, an ORR of 45% that excludes a 20% ORR at the 0.025 significance level would indicate meaningful efficacy in this highly refractory population.

The final analysis of the primary endpoint will be performed after all patients infused with CTL019 have completed 3 months follow-up from study day 1 infusion or discontinued earlier. The sample size for the final analysis of the primary endpoint will be up to 76 patients.

Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR > 20%, 76 patients in the FAS will provide more than 95% power to demonstrate statistical significance at one-sided 0.025 level of significance, if the underlying ORR is 45%, taking into account the interim analysis as described in Section 10.7. In this setting, an ORR of 30% (=23/76) will be needed to claim success.

Within the expected sample size of 76 patients with CTL019, at least 10 patients will be treated with CTL019 manufactured by the Fraunhofer Institute. If there are at least 6 patients among them who achieved best overall response of CR or CRi, the lower bound of the 95% confidence interval will be higher than 20%. The probability of observing at least 6 CR or CRi among the 10 patients will be 26% if the true ORR is 45%, and will be 84% if the true ORR is 70%.

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Table 10-5 Confidence intervals for ORR in patients infused with CTL019 manufactured by the Fraunhofer Institute

Total number of patients	CR + CRi	95% Exact CI
10	5	(18.7%, 81.3%)
	6	(26.2%, 87.8%)
	7	(34.8%, 93.3%)
	8	(44.4%, 97.5%)
	9	(55.5%, 99.7%)
	10	(69.2%, 100%)

The actual number of patients to be enrolled will depend on the pre-infusion dropout rate. Limited data are available so far to provide robust estimate on the pre-infusion dropout rate. Assuming 20% to 25% enrolled patients will not be infused due to reasons such as CTL019 product manufacturing issues, worsening of patient's condition, etc., approximately 95 patients need to be enrolled respectively to reach the number of patients required.

Cohort 1 (US only)

With 10 treated patients in Cohort 1, the confidence intervals for ORR in Cohort 1 will be the same as that of patients infused with CTL019 manufactured by the Fraunhofer Institute (Table 10-5). That is, if there are at least 6 patients in Cohort 1 who achieved best overall response of CR or CRi, the lower bound of the 95% confidence interval will be higher than 20%. The probability of observing at least 6 CR or CRi among the 10 patients in Cohort 1 will be 26% if the true ORR is 45%, and will be 84% if the true ORR is 70%. Only one patient was enrolled in Cohort 1 at the time of termination.

Cohort 2 (US only)

The purpose of Cohort 2 is to treat at least 5 patients which received CTL019 within 6 months from allo-HSCT to obtain clinical experience (feasibility and safety) in this group of patients. The data will be analyzed descriptively only. No patient was enrolled in Cohort 2 at the time of enrollment termination.

10.9 Power for analysis of key secondary variables for Main Cohort

10.9.1 ORR within 3 months in patients infused with CTL019 from US manufacturing facility

The same efficacy is assumed for patients infused with CTL019 in US manufacturing facility vs other manufacturing facilities. Under this assumption and conditional on the statistical significance of the primary endpoint, the over power of this endpoint will be greater than 95%, taking in account an interim analysis will be performed with first 50 patients, and then a final analysis will be performed with up to 66 patients with CTL019 from US manufacturing facility.

10.9.2 Remission with MRD negative bone marrow in patients who received CTL019 from all manufacturing facilities

In previous studies in the r/r ALL setting, 67% to 82% patients achieved MRD negative status among patients who achieved CR or CRi (Topp et al 2015, O'Brien et al 2012). Considering

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that an ORR of 45% that excludes 20% at the 0.025 significance level would indicate meaningful efficacy for ORR, 34% of patients achieving MRD negative bone marrow that excludes 15% at the 0.025 significance level would indicate meaningful efficacy (i.e. 75% among complete responders) for the key secondary objective.

Based on the above assumptions, conditional on the statistical significance of the primary and the first key secondary endpoint, and taking into account the interim analysis with first 50 patients as described above, up to 76 patients in the FAS will provide greater than 95 % power to demonstrate statistical significance at one-sided 0.025 level of significance, if the underlying percentage of patients who achieve BOR or CR or CRi with MRD negative bone marrow is 34%.

10.9.3 Remission with MRD negative bone marrow in patients who received CTL019 from US manufacturing facility

The same efficacy is assumed for patients infused with CTL019 in US manufacturing facility vs other manufacturing facilities. Under this assumption and conditional on the statistical significance of the primary and first 2 key secondary endpoints, the power of this endpoint will be 94%, taking in account an interim analysis will be performed with first 50 patients, and then a final analysis will be performed with up to 66 patients with CTL019 from US manufacturing facility.

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 International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), 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/assent 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 or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the

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patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent/assent 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/assent should be documented in the patient source documents. The date when a patient's informed consent/assent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) and assent form that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF/assent 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.

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

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.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g.www.clintrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted to novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e. LPLV); those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to

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present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to novartis.com.

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 patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

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 eCRFs 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 the 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.

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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 manufacture CTL019 product provided to limited personnel at the manufacturing facility. Signed informed consent/assent 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 treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

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

12.1 Amendments to the protocol

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

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[redacted]

14 Appendices

14.1 Appendix 1: Guidelines for efficacy evaluation in Acute Lymphoblastic Leukemia (ALL) studies

Document history

Version	Date	Changes
Draft v1.0	26-Jul-2013	First draft version for SPA
Draft v2.0	2-Dec-2013	Second draft version for SPA • CSF assessment by LP is required to establish CR or CRi for the first time • If there is extramedullary disease captured by physical exam, results will be classified by suspicion for leukemic involvement • Clarify the population for time to event variable analysis • For the analysis of DOR and other time to event endpoints, recommend to perform primary analysis by censoring SCT and sensitivity analysis by ignoring SCT • Add recommendation of sensitivity analysis of DOR considering death due to ALL as a competing risk • Clarify that for EFS patients who do not achieve complete response (CR or CRi) will be considered to have had an event on Day 1. Furthermore, patients who withdraw consent or are lost to follow-up will be censored in EFS analysis (rather than being considered to have had an event) • Other minor editorial changes
Draft v3.0	17-Jan-2014	Third draft version for SPA • Remove wording regarding acute lymphoblastic lymphoma because they will be excluded from the population to study • Revise wording regarding “clinical evidence of relapse” which is determined by peripheral blood assessment and extramedullary assessment (physical exam and CNS symptom assessment) • For the analysis of DOR, “death due to reason other than ALL” will be considered as a competing risk event for primary analysis
Draft v4.0	7-Mar-2014	Final version for SPA
Final v1.0	5-Mar-2014	First final version
Final v1.1	23-Dec-2014	Change the calculation of overall response date so that if the overall response classified as “No response”, the date of overall response will be calculated as the earliest of any component that reveals lack of response.
Final v1.2	26-Aug-2015	• Clarify that the qualitative assessment of tumor involvement will be used to determine response status when no blast count result is available from either bone marrow biopsy or aspirate. • Clarify that peripheral blood can be considered to be in remission status when bone marrow is in remission status at the same time. • Change the baseline disease assessment definition to indicate that the most current assessments within the protocol specified window will be used

[redacted]

Version	Date	Changes
Final v1.3	23-Feb-2016	• Remove the wording of Trilineage Hematopoiesis in the response assessment because the criteria for assessment, rigorous, and reproducible documentation of “trilineage hematopoiesis” in the marrow has not been well established. This can alternately be supported, in a reproducible and quantitative manner, by the use of peripheral blood platelet and neutrophil minimum values in the absence of transfusion of these blood components. • Change the baseline disease assessment definition to indicate that the most current assessment prior to enrollment/randomization will be used. Given the potentially long interval between enrollment and infusion of CTL019, more restricted time interval definition of baseline disease assessment is now implemented.

[redacted]

List of abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASH	American Society of Hematology
CHMP	Committee for Medicinal Products for Human Use
CR	Complete remission
Cri	CR with incomplete blood count recovery
(e)CRF	(electronic) case report form
CSF	Cerebral spinal fluid
CT scan	Computed Tomography scan
DOR	Duration of response
EFS	Event-free survival
FDA	United States Food and Drug Administration
IWG	International Working Group
LP	Lumbar puncture
mcL	Micro liter
MNC	Mononuclear cells
MRD	Minimal residual disease
NCI-WG	National Cancer Institute-Working Group
NCCN	National Comprehensive Cancer Network
ORR	Overall remission rate
OS	Overall survival
PR	Partial remission
RAP	Report and Analysis Plan
RBC	Red blood cell
PQ-PCR	Real-time quantitative polymerase chain reaction
RFS	Relapse-free survival
SCT	Stem cell transplant
SPD	Sum of the product of the diameters
TOC	Table of Contents
TTR	Time to remission
WBC	White blood cell

[redacted]

14.1.1 Introduction

This document provides the working definitions and specifications for a consistent and efficient analysis of efficacy for CTL019 clinical studies assessing antineoplastic activity in adult and pediatric acute lymphoblastic leukemia (ALL). The current document is written primarily for the relapse and refractory disease setting. Modifications may be indicated for earlier disease settings.

This document is based on the standardized response criteria defined by National Comprehensive Cancer Network (NCCN) Guidelines (NCCN 2013 v1) and further supported by the workshop report on acute leukemia from American Society of Hematology (ASH) (Appelbaum et al 2007) and the International Working Group (IWG) guideline for acute myeloid leukemia (AML) (Cheson et al 2003).

The Cheson IWG guideline and Appelbaum ASH report were used in recent drug approvals (e.g. Marqibo) in ALL, prior to the NCCN guideline availability. The NCCN guidance is a more recently published United States based guideline for ALL.

The objectives of this document are to:

- Ensure that the definitions of responses in a clinical study protocol correctly reflect the above mentioned guidelines.
- Provide guidance for the response assessment and clinical monitoring to ensure consistency in applying the guidelines.

Moreover, this document describes data handling and derivation rules. Respective sections may be used in the report and analysis plan (RAP) to provide further details. Relevant sections of this document will be copied into individual clinical trial protocols as appendix to the protocol.

14.1.2 Efficacy evaluation

Efficacy assessments are based on bone marrow and blood morphologic criteria, physical examination findings, along with laboratory assessments of cerebral spinal fluid (CSF) and bone marrow minimal residual disease (MRD) assessment. Radiologic assessments are used only in specific settings as defined below. It needs to be clearly specified in the protocol which response categories are considered as primary. Selection criteria for choosing efficacy endpoints should reflect the study setting accordingly.

14.1.2.1 Types of efficacy assessments

Disease characterization at baseline and evaluation of response rely on the following:

- Bone marrow assessment
- Peripheral blood assessment
- Extramedullary disease assessment, including
  - CNS disease
  - Other extramedullary sites
- Minimal residual disease (MRD) assessment of bone marrow

For timing and window of the disease assessments for response classification, see Section 14.1.2.3.1 for details.

[redacted]

14.1.2.1.1 Assessment of bone marrow blast counts

Bone marrow will be assessed for blast cells. Percentage of blast cells will be determined by morphologic or cytologic examination. This assessment can be performed on bone marrow biopsy and/or aspirate. If the blast counts are assessed, results from these assessments are considered to be interchangeable. Some laboratories do not perform differential counts on bone marrow biopsies, but rather provide a qualitative assessment whether there is tumor involvement or not: i.e. Yes or No tumor (blast) cells are seen in the bone marrow biopsy section or the touch print from the bone marrow biopsy. In this case, it may not be possible to definitively determine whether the blast count is <5% or not.

Both bone marrow biopsy and aspirate tests will be considered for response assessment as follows:

- In the case of only one assessment with non-missing blast count values: Result of the non-missing assessment will be used.
- In the case of both assessments with differing, non-missing blast count values: The highest blasts value will be considered. The corresponding assessment date will be used as reference for other assessments for the determination of evaluation windows.
- In the case of no blast count values available from either aspirate or biopsy, but a qualitative assessment of tumor involvement from biopsy is available: The bone marrow result will be considered to be in remission if there is no tumor involvement, and will be considered to indicate no response or relapsed disease if there is tumor involvement.
- In the case of no blast count values available from either aspirate or biopsy, and no qualitative assessment of tumor involvement from biopsy is available: The bone marrow result will be considered as “unknown”.

14.1.2.1.2 Assessment of peripheral blood

All values must be taken from the same blood sample. Relevant variables are platelet and neutrophil counts and percentage of leukemic blasts. Recent transfusion status also has to be taken into account (See Section 14.1.2.3.3 for details).

If the peripheral blood count is so low that a differential count cannot be obtained (e.g. typically when WBC < 0.5 x 10^9/L preventing an accurate assessment of differential count), but the bone marrow result is showing complete remission status (per definition in Table 14-1). In this case, the patient will also be considered to be in remission status in peripheral blood.

14.1.2.1.3 Assessment of extramedullary disease

Extramedullary involvement is to be assessed at baseline and at each visit for response assessment. Presence or absence and physical location of extramedullary disease is to be captured in the (e)CRF.

Extramedullary disease is to be assessed via physical examination, CSF assessment, and if clinically appropriate relevant imaging techniques. In case of extramedullary disease at baseline or (re-)appearance during the study, the lesions should be considered for confirmation by imaging or biopsy if technically and/or clinically feasible.

[redacted]

14.1.2.1.3.1 Assessment of CNS disease

Baseline CSF assessment by lumbar puncture (LP) is mandatory. The frequency and timing of post-baseline CSF assessment may depend upon the study setting and standard of care for each setting (e.g. front line or relapse/refractory, pediatric vs adult, etc.) and should be clearly specified in the protocol. At a minimum, lumbar puncture should be performed as clinically indicated by the presence of neurologic symptoms.

The classification of CNS status includes the following:

- CNS-1 refers to no lymphoblasts in the CSF regardless of WBC count;
- CNS-2 is defined as WBC less than 5/mcL in CSF with presence of lymphoblasts;
- CNS-3 is defined as WBC of 5/mcL or greater with presence of lymphoblasts.

If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC ≥ 5/mcL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

CNS remission is defined as achievement of CNS-1 status in a patient with CNS-2 or CNS-3 at initial assessment.

CNS relapse is defined as development of CNS-3 status or development of clinical signs of CNS leukemia (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome, etc.). If clinical signs of CNS leukemia exist, it must be confirmed by CNS imaging (CT or MRI of brain) or other relevant methods (e.g. biopsy, LP, etc.) to define CNS relapse.

14.1.2.1.3.2 Assessment of mediastinal disease

Radiographic assessments are not standard components for routine disease assessments of acute lymphoblastic leukemia (NCCN 2013 v1, Cheson et al 2003).

The classification of mediastinal response in NCCN 2013 v1 based on radiographic assessments is hence not applicable for studies where only acute lymphoblastic leukemia patients are studied.

14.1.2.1.3.3 Assessment of other extramedullary disease

The assessment of other extramedullary disease (hepatomegaly, splenomegaly, skin/gum infiltration, testicular mass or other masses) will be performed via physical exam.

Hepatomegaly and splenomegaly due to leukemic involvement, disease involvement by lymph nodes, infiltration of the skin or gums, unilateral or bilateral testicular mass, or other masses will be assessed by physical exam. Results will be coded as “Normal”, “Abnormal with no or low suspicion for leukemic involvement”, or “Abnormal with high suspicion for leukemic involvement”. The rationale for these three categories is as follows. Other abnormalities that are not related to leukemic infiltration can often be observed in these organ sites on physical examination in patients with ALL, especially during the first 28 days after lymphodepleting chemotherapy followed by CTL019 cell infusion. Definitive proof of leukemic infiltration (e.g. liver biopsy) is often not definitive, indicated or ethically justified. Some abnormalities may occur (e.g. ecchymosis in skin or gums, acute/transient hepatosplenomegaly associated with acute infections or Macrophage Activation Syndrome (MAS)) but are clearly not leukemic

[redacted]

involvement. Therefore three categories will more accurately capture these different clinical scenarios. In the analysis, "Normal" or "Abnormal with no or low suspicion for leukemic involvement" will be considered eligible for overall CR or CRi assessment; "Abnormal with high suspicion for leukemic involvement" will not be considered eligible for overall CR or CRi assessment, and will be considered to trigger relapsed disease assessment. Serial physical examinations for these assessments will be performed (at protocol specified frequency) to validate the persistence or resolution of such findings.

Lymph nodes on physical exam are considered to be abnormal if greater than 1.5 cm. Note that although the cutoff of 1.5 cm is not defined in the NCCN (NCCN 2013 v1) or the Cheson guidelines (Cheson et al 2003), it is used in the international harmonization project revised response criteria for lymphoma (Cheson (2007a) and Cheson (2007b)) and the international working group guideline for chronic lymphocytic leukemia (Hallek et al 2008).

14.1.2.1.4 Assessment of minimum residual disease (MRD) in bone marrow

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods. Patients who experienced a CR according to morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow: up to 10^{10} malignant cells which can confer a poor outcome. The most frequently used methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and PCR assays to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes or fusion transcripts (e.g. BCR-ABL). Current flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-4} (<0.01%) [redacted] The concordance rate for detecting MRD between these methods is high. Numerous studies in childhood and adult ALL have shown the prognostic importance of post-induction (and/or post-consolidation) MRD measurements in predicting the likelihood of disease relapse. The timing of MRD assessment varies depending on the ALL treatment protocol and the disease setting (e.g. initial/up front treatment vs relapse/refractory). For MRD evaluation on multicolor flow cytometry, sampling of bone marrow MNCs is preferred over peripheral blood samples. At least 1×10^6 MNCs are required for analysis (≈ 2 mL of bone marrow or 5–10 mL of peripheral blood provides sufficient number of cells for multiple analysis). For MRD evaluation with real-time quantitative PCR (RQ-PCR), sampling of bone marrow MNC is preferred. At least 1×10^7 MNCs are required for initial marker characterization and generation of individual dilution series; 1×10^6 MNCs are sufficient for follow-up analysis. The minimal limit of assay sensitivity (to declare MRD negativity) should be less than 1×10^{-4} (< 0.01%).

For Ph+ ALL, BCR-ABL quantitative PCR may also be used to assess MRD status.

The timing of MRD assessment is dependent upon the disease setting and should be specified in the protocol.

MRD assessment by flow cytometry or RQ-PCR should be performed via a central certified lab with 0.01% sensitivity. MRD by [redacted]

14.1.2.2 Baseline evaluation

The following baseline assessments are mandatory:

[redacted]

- Bone marrow biopsy and/or aspirate for blast cell counts (Section 14.1.2.1.1)
- Peripheral blood for blast, neutrophil and platelet cell counts (Section 14.1.2.1.2)
- CSF cytology via lumbar puncture for WBC, RBC cell and lymphoblast numbers (Section 14.1.2.1.3.1)
- CNS imaging (CT or MRI) or other appropriate assessment if clinical signs of CNS leukemia exist (Section 14.1.2.1.3.1)
- Physical exam for extramedullary disease (Section 14.1.2.1.3.3)
- Blood and bone marrow MRD assessment by flow cytometry (Section 14.1.2.1.4)
- Cytogenetics and/or FISH from bone marrow aspirate

For disease characterization at baseline, the most current assessments (bone marrow, blood count, CSF, physical exam, etc.) on or prior to the date of enrollment/randomization should be used as the baseline assessment.

14.1.2.3 Post-baseline overall disease response evaluation

14.1.2.3.1 Components and timing of overall disease response evaluation

The initial achievement of CR or CRi will require evaluation of remission in bone marrow, peripheral blood, and the absence of extramedullary disease. Following initial achievement of CR or CRi, if the patients have normal peripheral blood, physical exam and no CNS symptoms, they will be considered to remain in clinical CR or CRi, i.e. there is no clinical evidence of relapse (Section 14.1.2.3.4).

An overall disease response evaluation must consist all of the following components:

- Peripheral blood for morphologic blast, neutrophil and platelet cell counts (Section 14.1.2.1.2)
- CNS symptom assessment (Section 14.1.2.1.3.1)
- Physical examination for extramedullary disease (Section 14.1.2.1.3.3)

In addition,

- Post-baseline bone marrow biopsies and/or aspirates (Section 14.1.2.1.1) for morphologic blast cell counts are required to demonstrate that a patient has achieved CR or CRi for the first time. Following initial achievement of CR or CRi, a bone marrow biopsy or aspirate will not be required unless it is clinically indicated (e.g. worsening of platelet or neutrophils; reappearance of blast in peripheral blood, etc.) or as specified per individual protocol.
- Post-baseline CSF cytology via lumbar puncture (Section 14.1.2.1.3.1) is required to demonstrate that a patient has achieved CR or CRi for the first time. Following initial achievement of CR or CRi, a lumbar puncture will not be required unless it is clinically indicated by the presence of neurologic symptoms and as specified per individual protocol.
- MRD assessment (Section 14.1.2.1.4) should be performed per protocol specification.

In order for all components of disease assessments to be qualified as the same response evaluation, peripheral blood sample collection, CNS symptom assessment, physical exam, bone

[redacted]

marrow biopsy/aspirate (if needed) and lumbar puncture (if needed) need to be performed, in general, within 14 days of each other, unless specified otherwise in the protocol.

In case of missing data for the full evaluation required to qualify for a certain response category, the overall evaluation "unknown" will be assigned unless at least one observation was made which qualifies for relapse. Relapse can be determined by the relapsed component alone.

Also see Section 14.1.2.3.2 and Section 14.1.2.3.4 for the definition and confirmation of disease response.

The frequency of response evaluation for each component needs to be clearly specified in the protocol. The timing should be coordinated so that a full response evaluation can be made.

14.1.2.3.2 Response criteria

The overall disease response is determined at a given evaluation using the criteria described in Table 14-1. Note that:

- The NCCN guidance (NCCN 2013 v1) has defined a progressive disease (PD) category. In this document, PD is considered the same as "No response", which is consistent with Cheson et al (2003) guideline. The difference between PD and "No response" in ALL is not believed to be clinically meaningful.
- See Section 14.1.2.1.1 for details regarding assessing bone marrow response status.

[redacted]

Table 14-1 Overall disease response classification at a given evaluation time

Response category	Definition
Complete remission (CR)	All the following criteria are met: **Bone marrow** • < 5% blasts **Peripheral blood** • Neutrophils > 1.0 x 10^9/L, and • Platelets > 100 x 10^9/L, and • Circulating blasts < 1% **Extramedullary disease** • No clinical evidence of extramedullary disease (by physical exam and CNS symptom assessment) and • If additional assessments (e.g. CSF assessment by LP, CNS imaging, biopsy, etc.) are performed, results must show remission status **Transfusion independency** (see Section 14.1.2.3.3). • No platelet and/or neutrophil transfusions less than or equal to 7 days before the date of the peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	All criteria for CR as defined above are met, except that the following exist: • Neutrophils ≤ 1.0 x 10^9/L, and/or • Platelets ≤ 100 x 10^9/L, and/or • Platelet and/or neutrophil transfusions less than or equal to 7 days before the date of the peripheral blood sample for disease assessment
No response	Failure to attain the criteria needed for any response categories or relapse
Relapsed Disease	Only in patients who achieved a CR or CRi and who have: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi
Unknown	"Unknown" is assigned in case the baseline assessment or the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame (Section 14.1.2.2 and Section 14.1.2.3.1). If there is evidence of relapse, the overall response will assessed as "relapsed disease" with the relapsed component alone.

14.1.2.3.3 Evaluation of transfusion dependency

Information on transfusion dependency will be assessed at baseline as well as during the course of the trial for all patients. Transfusion of blood products will be recorded in a separate module of the (e)CRF. The type of transfusion, start and end date as well as the volume of blood product will be captured at each visit with hematologic assessment.

A period of at least one week (7 days) without any transfusion has been taken as a convention to define the status of transfusion independence to assess a CR vs CRi response (Cheson et al 2006). Any sample of peripheral blood sample for disease assessment which was taken less than or equal to seven days after a transfusion will be considered as transfusion dependent.

14.1.2.3.4 Establishing CR/CRi and subsequent maintenance of CR/CRi with no clinical evidence of relapse

A full response evaluation, including assessments of peripheral blood, bone marrow, CNS symptoms, physical exam and CSF assessment by LP, is required at the first time a CR or CRi

[redacted]

is demonstrated (Section 14.1.2.3.1). Bone marrow biopsy/aspirate and CSF assessment by LP are required 1 month (Day 28) after infusion. If the patient is not in CR/CRi at Month 1, then a bone marrow biopsy/aspirate and CSF assessment by LP are also required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) to establish that a patient has achieved CR/CRi for the first time. Additional bone marrow biopsies/aspirates and CSF assessments by LP may be recommended in the protocol.

Complete remissions in patients with ALL have been observed to take place within 1 month after infusion with CTL019. The onset of complete remissions are rapid and dramatic, and patients quickly regain a normal performance status. ALL relapse in the bone marrow is rapidly followed by signs or symptoms of disease recurrence as well as abnormalities in the peripheral blood.

Therefore, following initial achievement of CR/CRi, patients will be considered to have maintained a clinical CR/CRi if the patient has no evidence of extramedullary disease (by physical exam and CNS symptom assessment) and circulating blasts in peripheral blood are <1%.

In order for the best overall disease response to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. Please note, if additional assessments (e.g. bone marrow, CSF assessment by LP, CNS imaging, biopsy, etc.) are performed (Section 14.1.2.3.1) in the same evaluation for disease response evaluation purpose, they will also need to show remission status.

The onset date of CR or CRi will then be derived as the evaluation date of the initial CR or CRi assessment. If a patient satisfied CRi at one evaluation and later confirmed as a CR in the next evaluation, the patient will be considered as having confirmed CR. However, the date of CR will be derived as the latter (confirmed) evaluation date.

14.1.2.3.5 Date of overall disease response evaluation

A complete evaluation of response includes at the minimum the assessments of peripheral blood, CNS symptoms and physical exam. In addition, bone marrow and CSF assessment may be required. All components of disease assessments must be performed within the specified time frame (Section 14.1.2.3.1) to be qualified as the same response evaluation.

If the overall disease response is CR, CRi, or Unknown, the evaluation date (i.e. for one evaluation number) is defined as the latest of all dates of required measurements at that evaluation number. This rule applies also in case of multiple measurements of the same variable.

Relapse or No response can be assessed based on a partial evaluation (e.g. a relapse is assessed from blood alone). The assessment date for relapse or no response is calculated as the earliest date of all assessments that reveal a relapse or lack of response.

[redacted]

14.1.3 Data collection

14.1.3.1 Data sources

The summary of data sources refers to disease-specific (e)CRF standard modules. It is not appropriate to deviate from these specifications in Table 14-2.

Table 14-2 Data sources

(e)CRF module	Specification
Overall disease response	Overall disease response and assessments of individual components from • bone marrow; • blood; • CNS disease; • other extramedullary disease.
Bone marrow biopsy / aspirate	Aspirate or biopsy; morphologic blast counts and MRD assessment.
Blood response	Response status for platelets, neutrophils, morphologic blast counts; status of platelet and/or neutrophils transfusion.
CSF assessment [1]	CSF lymphoblast, WBC, RBC
Other CNS disease	CNS symptoms, confirmation of CNS disease via imaging or other methods (if applicable)
Extramedullary disease by physical exam	Presence/absence, location, method of assessment, confirmation by biopsy or imaging or not if feasible
Blood component transfusions	Type and number of units of transfusions, timing with respect to disease assessment
Hematopoietic Stem Cell Transplant (SCT) – post infusion	Date, type of post-treatment SCT

[1] When there is clinical signs of CNS disease and/or at protocol specified time points

14.1.3.2 Recording response evaluation on the (e)CRFs

The components and timing needed to adequately assess overall disease response is outlined in Section 14.1.2.3.1. In practice, disease response evaluation (either a complete assessment or only some components) may be performed on both scheduled and unscheduled time points. Also it is not uncommon in oncology trials that disease responses are sometimes assessed at time points not matching the scheduled time points. For example, when a patient's condition prevents certain assessments, the scheduled evaluation will have to be delayed to a later time point.

As a result, the recording of response evaluation is aligned using the "Evaluation number" on the (e)CRFs. A new evaluation number should be assigned whenever a scheduled or unscheduled disease response assessment is performed, and hence is not necessarily aligned with the study visits.

When relapse can be judge based on any component. E.g. if a relapse is observed from blood sample alone without bone marrow assessment etc. at any time, it will be recorded on the (e)CRFs, with all other assessments as "not done" or "unknown".

See also Section 14.1.2.3.5 regarding assigning date of the overall response.

[redacted]

14.1.3.3 Capturing overall response evaluation

Data monitoring reports will be prepared to identify investigator's assessments which differ from calculated response based on the rules of this document. This discrepancy may be queried for clarification. However, the investigator's response will not be overruled in any case.

14.1.4 Efficacy analysis definitions

14.1.4.1 Local vs central evaluation of efficacy

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

- Investigator overall disease response based on local radiological assessments, local clinical, pathological (e.g. bone marrow) and laboratory response.
- Central review based on review of the totality of the source data by an independent review committee (IRC).

The Study Protocol should state which evaluation source will be used for the primary analysis.

14.1.4.2 Best overall disease response

The best overall disease response is the best disease response recorded from **randomization/first CTL019 infusion** until start of new anticancer therapy.

Best response will be assigned according to the following order:

1. CR
2. CRi
3. No response
4. Unknown

The best overall disease response for a patient is always calculated, based on the sequence of overall disease responses. For the best overall disease response to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi, as explained in Section 14.1.2.3.4.

The overall remission rate (ORR) is defined as the proportion of patients with a best overall disease response of CR or CRi.

14.1.4.3 Time-to-event definitions

General rule for the calculation of the time to event interval is:

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

When no post-baseline response assessments are available, the date of **randomization/first CTL019 infusion** will be used as event date when time is to be censored at last post-baseline response assessment, i.e. time to event variables will never be negative.

Often censoring time is determined based on date of adequate response assessment. Any response assessment is considered to be adequate if the assessment was performed and the outcome of the assessment was other than "unknown" or "not done".

[redacted]

14.1.4.3.1 Overall survival (OS)

Overall survival (OS) is the time from date of **randomization/ first CTL019 infusion** to the date of death due to any reason.

In case a patient is alive at the date of last contact on or before data cutoff, OS is censored at the date of last contact. The handling of SCT for the calculation of OS must be clearly specified in the protocol. See also Section 14.1.4.4 for more discussion.

OS will be assessed in all patients (FAS).

14.1.4.3.2 Duration of remission (DOR)

Duration of remission (DOR) is defined as the duration from the first documented onset of CRi or CR to the date of relapse or death due to ALL.

In case a patient does not have relapse or death due to ALL 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
- Event after at least two missing scheduled disease assessment

In addition, death due to reason other than ALL can be considered as either a competing risk event to other events of interest (relapse or death due to ALL), or a censoring event. The protocol should clearly specify which analysis is used as the primary analysis for DOR.

Since patients in remission might choose to receive SCT, censoring due to SCT will overestimate the risk of relapse and therefore may be considered inappropriate for the main analysis, when there is a substantial number of patients choose to receive SCT (CHMP 2010). The handling of SCT for the calculation of DOR must be clearly specified in the protocol.

See also Section 14.1.4.4 for more discussion.

DOR will be assessed only in patients with the best overall response of CR or CRi.

14.1.4.3.3 Relapse-free survival (RFS)

Relapse-free survival (RFS) is measured by the time from achievement of CR or CRi whatever occurs first to relapse or death due to any cause during CR or CRi.

In case a patient does not have relapse or death due to any cause prior to data cutoff, RFS 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

[redacted]

- Event after at least two missing scheduled disease assessment

The handling of SCT for the calculation of RFS must be clearly specified in the protocol.

See also Section 14.1.4.4 for more discussion.

RFS will be assessed only in patients with the best overall response of CR or CRi.

14.1.4.3.4 Event-free survival (EFS)

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

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

In case of treatment failure, the event date will be set to study Day 1 (CHMP 2010).

In case a patient does not experience an event (e.g. discontinuation as a result of withdrawal of consent, lost to follow-up, protocol violation or administrative problems) prior to data cutoff, EFS is censored at the last adequate response assessment date 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
- Event after at least two missing scheduled disease assessment

The handling of SCT for the calculation of EFS must be clearly specified in the protocol.

See also Section 14.1.4.4 for more discussion.

EFS will be assessed in all patients (FAS).

14.1.4.4 Event and censoring date, sensitivity analyses

This section outlines the possible event and censoring dates for relapse (Table 14-3), addresses the issues of missing response assessments during the study, and the options for handling new anticancer therapy. It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of sensitivity analyses to be performed.

SCT is a standard treatment option for ALL patients. For time-to-event endpoints it needs to be specified in the protocol how patients who choose to undergo SCT following study protocol treatment will be handled for analysis.

[redacted]

Using the draft FDA guideline (2007) on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics) and the EMA guideline on the evaluation of Anticancer Medicinal Products in Man on Confirmatory studies in Haematological Malignancies (CHMP 2010) as references, the following analyses can be considered:

Table 14-3 Options for event dates used in DOR, EFS and RFS

Situation		Options for event date (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment	Censor
B	Relapse at scheduled assessment date or before next scheduled assessment	(1) Date of relapse	Event
		(2) Date of next scheduled assessment	Event
C1	Relapse after exactly one missing assessment	(1) Date of relapse	Event
		(2) Date of next scheduled assessment	Event
C2	Relapse after two or more missing assessments	(1) Date of last adequate assessment	Censor
		(2) Date of next scheduled assessment	Event
		(3) Date of relapse	Event
D	New anticancer therapy given (excluding SCT)	(1) Date of last adequate assessment	Censor
		(2) Date of secondary anti-cancer therapy	Censor
		(3) Date of secondary anti-cancer therapy	Event
		(4) N/A	Ignored
E	SCT	(1) Date of SCT	Censor
		(2) N/A	Ignored
		(3) Date of SCT	Competing Risk Event
		(4) Date of last adequate assessment prior to SCT	Censor
F	Death due to reasons other than ALL (for DOR only)	(1) Date of death	Competing Risk Event
		(2) Date of last adequate assessment	Censor

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

Situations C (C1 and C2): Relapse or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

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

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

Situation D: New anticancer therapy (excluding SCT) given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment prior to new anticancer therapy may be used as a default in this case.

[redacted]

Situation E: As SCT is an important treatment option in responding patients, it is appropriate to consider the date of SCT as censoring date, instead of censoring at the last tumor assessment date. However, censoring due to SCT will overestimate the rate of relapse and therefore may be considered inappropriate for the default analysis when a substantial number of patients choose to receive SCT. Analysis ignoring SCT should be considered (CHMP 2010).

Since SCT during remission after the experimental treatment may affect the risk of relapse, a sensitivity analysis may be considered in which SCT is regarded as a competing risk to the event of interest (e.g., relapse after the experimental treatment). In this analysis, the cumulative incidence function (CIF), instead of the usual KM, is used to estimate the probability of remaining free of the event of interest in the presence of the competing risk (Kim 2007).

Situation F: Note that the KM method used to analyze DOR in the presence of censoring can be biased if the censoring event is not independent to the event of interest (i.e. relapse and death due to ALL). Therefore, analysis can also be performed considering death due to reason other than ALL as a competing risk event. In this case, the cumulative incidence function (CIF) instead of KM is used to estimate the probability of relapse in the presence of the competing risk (Kim 2007).

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-3 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and have to be specified in the study protocol or RAP documentation.

[redacted]

14.1.5 References (available upon request)

Appelbaum FR, et al. (2007) End points to establish the efficacy of new agents in the treatment of acute leukemia. Blood 109: 1810-1816

Cheson B, Bennet JM, Kopecky K, et al. (2003) Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Journal of Clinical Oncology; 21(24):4642-9

Cheson BD (2007a) The international harmonization project for response criteria in lymphoma clinical trials. Hematol Oncol Clin N Am 21:841-854

Cheson BD, Greenberg P, Bennett J, et al. (2006) Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood; 108: 419-425

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

CHMP (2010) Appendix 2 to the Guidance on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev. 3) on confirmatory studies in haematological malignancies

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

Hallek M, et al. (2008) Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood 111.12: 5446-5456

Kim H (2007) Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis. Clinical Cancer Research 2007;13:559-565

National Comprehensive Cancer Network (NCCN) Guidelines (NCCN, 2013 v1), Acute Lymphoblastic Leukemia

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

Table 14-4 Eligibility based on serologic markers for hepatitis B infection

Test	Results				
HBsAg	+	-	-	-	-
Anti-HBc	Any	+	-	+	-
Anti-HBs	Any	-	+	+	-
Eligibility	Not Eligible	Not Eligible	Eligible	Eligible	Eligible

If indeterminate results are obtained, viral DNA levels should be measured to confirm negative viral status.

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: Protective – Indicates vaccination or previous infection that has been successfully resolved. These patients are eligible for this trial.

HBsAg negative, Anti-HBc positive, Anti-HBs negative: Indicates latent infection. These patients are also at risk for viral reactivation. These patients are not eligible for this trial.

[redacted]

14.3 Appendix 3: CTL019 modified data reporting – Treatment and Primary Follow Up Phase

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 events, including all laboratory abnormalities deemed clinically significant by the investigator	• Modified –Whether serious or non-serious, report following: • Any SAE irrespective of grade • Events leading to death • Related to a study procedure • Infections • Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic 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 (≥ Grade 3) 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: • Anticytokine therapies (e.g. tocilizumab, or other) • Corticosteroids (including prophylactically for blood product administrations, physiologic replacement doses, high or stress doses, etc.) • Anti-seizure medications • Allopurinol, or non-allopurinol alternatives • Rasburicase • Immunoglobulin therapy • Any medication given therapeutically for an SAE • Vasopressors and cardiac inotropic agents (see below) • Narcotics and sedatives (see below) • Antineoplastic therapies (e.g. lymphodepeleting 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. ug/kg/hr, mg/hr, etc.) **Narcotics and sedatives:** • For dose, record only total daily dose **Blood products (e.g. red cells, platelets, FFP, cryoprecipitate):** • **If administered ≤7 days of a tumor response assessment:** o Record ALL blood products, including prophylaxis (to distinguish CR vs CRi) • **If NOT administered ≤7 days of a tumor response assessment:** o Only record blood products if given for bleeding (excludes prophylactic use) • Related to an AE or SAE defined as reportable for this period **Electrolyte & vitamin replacement:**		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**
	• Record all electrolyte replacement if given for a **≥ Grade 3** electrolyte disturbance and list these as an adverse event (AE). • Do **not** record ≤ Grade 2 or 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			

Laboratory data	Modified:
	• Record **all** scheduled labs (per Visit Evaluation Schedule)
	• Record **all** results (scheduled or unscheduled) for: LDH, Uric acid, CRP, Ferritin, and fibrinogen (related to CRS/TLS/MAS)
	• Record all other laboratory values if they are ≥ Grade 3
	• For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled)
	  • For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia)
	  • Laboratory abnormalities that are treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)
			All	Modified:
				• Record **all** scheduled labs (per Visit Evaluation Schedule)
				• Record **all** results (scheduled or unscheduled) for: LDH, Uric acid, CRP, Ferritin, and fibrinogen (related to CRS/TLS/MAS)
				• Record all other laboratory values if they are ≥ Grade 3
				• For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled)
				  • For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia)
				  • Laboratory abnormalities that are treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)

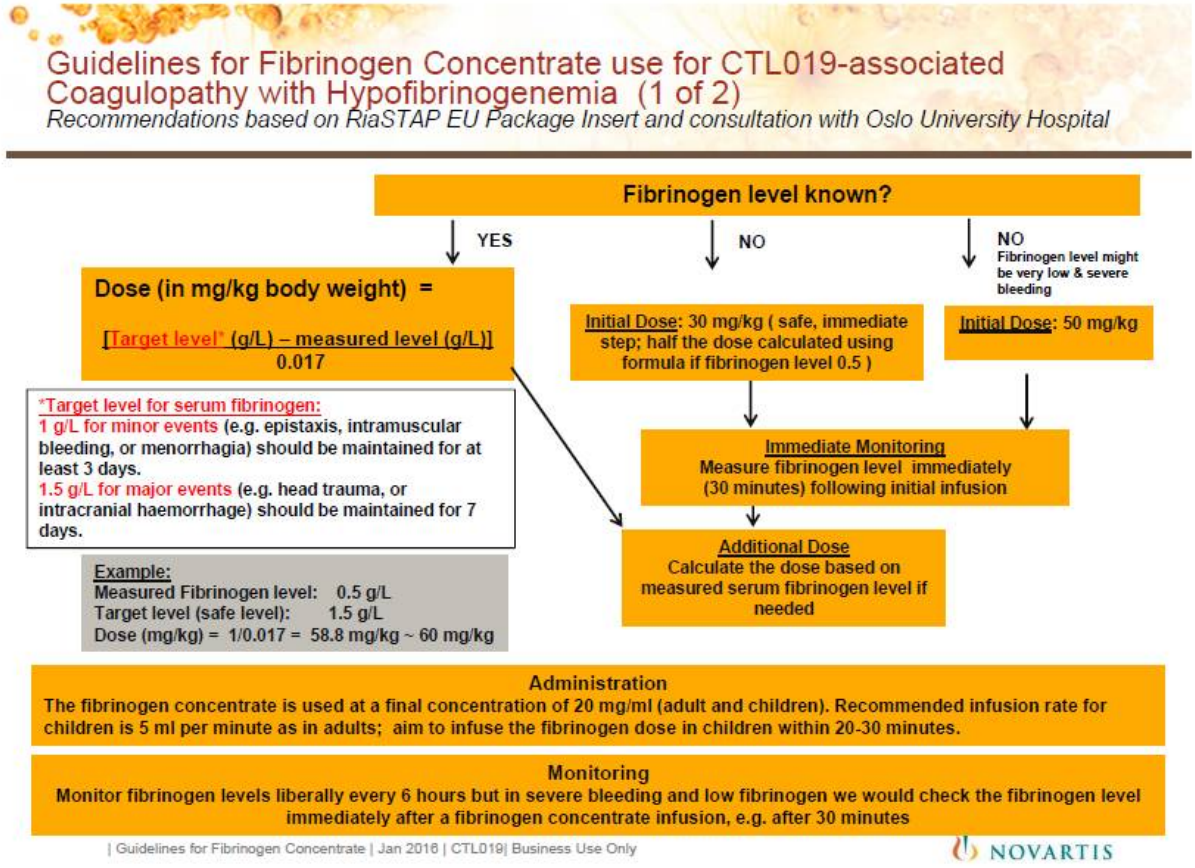
[redacted]

14.4 Appendix 4: 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 and the investigator assess a reasonable relationship to CTL019 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 primary malignancy • Progressive multifocal leukoencephalopathy (PML) • Hepatitis B reactivation	• Intravenous Immunoglobulin • For all patients who are in remission, the first antineoplastic therapy administered (first therapy including conditioning for cell therapy (CAR, SCT) plus cell therapy (CAR, SCT) should be reported. • Data to support adverse events may be requested

14.5 Appendix 5: [EU Only: Guidelines for use of fibrinogen concentrate in CTL019-associated coagulopathy with hypofibrinogenemia

If cryoprecipitate is not readily available guidance is being provided below on the use of fibrinogen concentrate for the management of CTL019 associated coagulopathy with hypofibrinogenemia. Note this guidance is for Norway, Spain, Austria and Italy only.



[redacted]

Guidelines for Fibrinogen Concentrate use for CTL019-associated Coagulopathy with Hypofibrinogenemia (2 of 2)*

** Based on experience at Oslo University Hospital (Jochen Büchner and colleagues)*

Reconstitution

- Reconstitute Riastap to a concentration of 20 mg/ml, for adults and children.
- Be gentle and do not shake, to avoid foam and bubbles. Reconstituting the lyophilized powder by aspirating the solution up and down into a syringe through a needle, or vigorous shaking, makes it impossible to dose a definite volume or infuse

Infusion

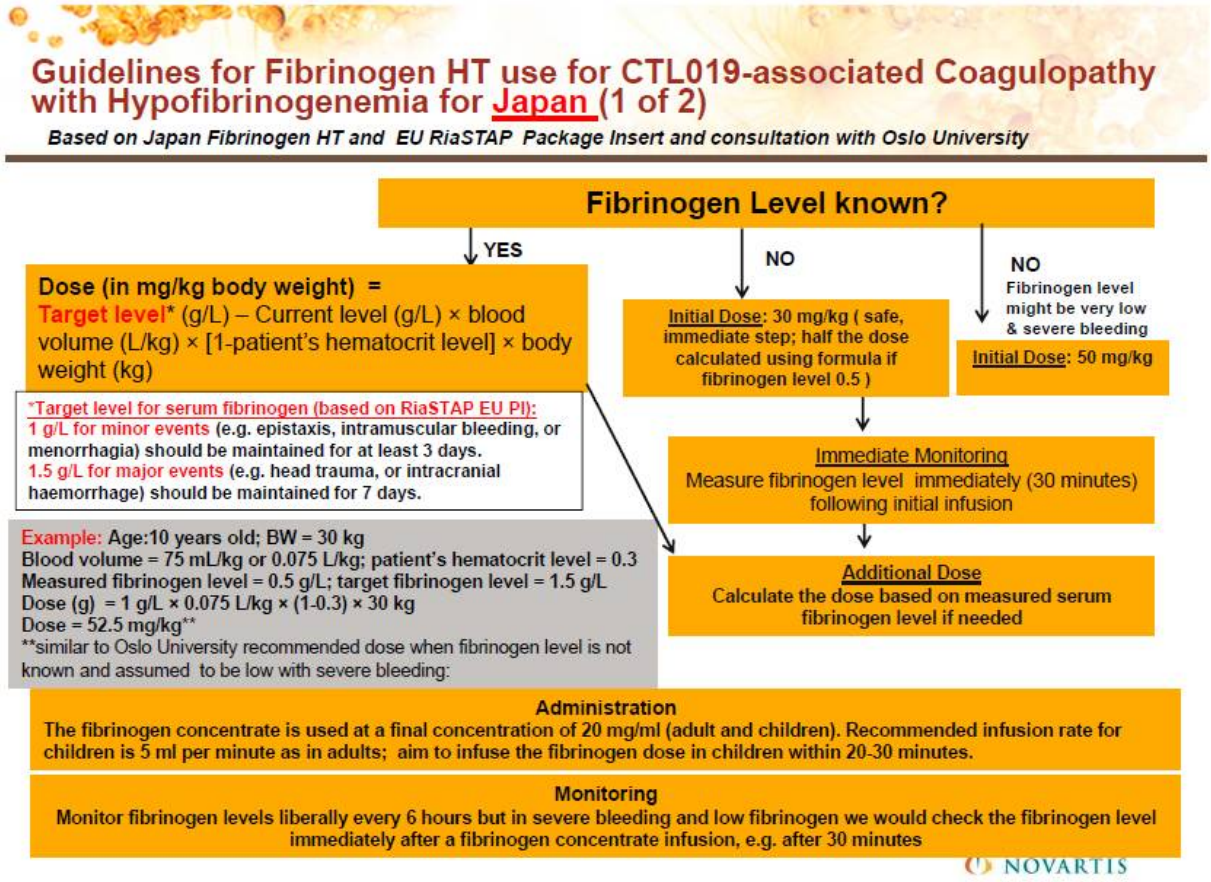
- 5 ml per minute rate has been safely used also for small children. Do not exceed 5 ml per min (maximum infusion rate of 100 mg/min)
- At Oslo site, Riastap has sometimes been given to children by manually infusing it within a few minutes into the central line, without seeing adverse reactions.
  - Example: a 10 kg child in need of 50 mg/kg Riastap = 500 mg would need 25 ml Riastap that would be infused in 5 min if an infusion rate of 5 ml/min is used.
- In Oslo, any dose for a child would be infused within a 20-30 minute period.

NOVARTIS

[redacted]

14.6 Appendix 6: [Japan Only: Guidelines for use of fibrinogen concentrate in CTL019-associated coagulopathy with hypofibrinogenemia]

If cryoprecipitate is not readily available guidance is being provided below on the use of fibrinogen concentrate for the management of CTL019 associated coagulopathy with hypofibrinogenemia. Note this guidance is for Japan only.



[redacted]

Guidelines for Fibrinogen HT use for CTL019-associated Coagulopathy with Hypofibrinogenemia for Japan (2 of 2)

Based on Japan Fibrinogen HT and EU RiaSTAP EU Package Insert and consultation with Oslo University

- Reconstitution

- 1 gram (g) Fibrinogen HT to 50 mL of water for injection resulting in 20 mg/mL of i.v. solution (same as EU product RiaSTAP). Reconstitute to a concentration of 20 mg/ml, for adults and children.
- Be gentle and do not shake, to avoid foam and bubbles. Reconstituting the lyophilized powder by aspirating the solution up and down into a syringe through a needle, or vigorous shaking, makes it impossible to dose a definite volume or infuse

- Infusion

- 5 ml per minute rate has been safely used also for small children. Do not exceed 5 ml per min (maximum infusion rate of 100 mg/min)
- At Oslo site, Riastap (EU product) has sometimes been given to children by manually infusing it within a few minutes into the central line, without seeing adverse reactions.
  - Example: a 10 kg child in need of 50 mg/kg Riastap = 500 mg would need 25 ml Riastap that would be infused in 5 min if an infusion rate of 5 ml/min is used.
- At Oslo University, any dose for a child would be infused within a 20-30 minute period.

7 NOVARTIS

[redacted]

14.7 Appendix 7: Liver and Laboratory trigger Definitions and Follow-up Requirements

Table 14-5 Liver Event and Laboratory Trigger Definitions

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

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

Table 14-6 Follow Up Requirements for Liver Events and Laboratory Triggers

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

[redacted]

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

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

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

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

[redacted]

14.8 Appendix 8: Specific Renal Alert Critiera and Actions end Event Follow-up

Table 14-7 Specific Renal Alert Criteria and Actions

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

[+]Corresponds to KDIGO criteria for Acute Kidney Injury

[redacted]

Table 14-8 Follow up 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