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List of abbreviations

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase/Serum Glutamic Pyruvic Transaminase/SGPT
ALP	Alkaline Phosphatase
Anti-HBc	Hepatitis B Core Antibody
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase/SGOT
AUC	Area Under the Curve
AV	Atrioventricular
B cell ALL	B-cell Lineage ALL
4-1BB	Type 2 Transmembrane Glycoprotein Belonging to the TNF Superfamily, Expressed on Activated T Lymphocytes
BCR-ABL	Philadelphia Chromosome
CABG	Coronary Artery Bypass Graft
CAR	Chimeric Antigen Receptor
CD	Cluster of Differentiation
CFR	Code of Federal Regulations
CHP	Children's Hospital of Philadelphia
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
C_{last}	Last Observed Quantifiable Concentration
C_{max}	Maximum Concentration
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CNS3	Classification Based on ≥ 5 WBCs in the Cerebrospinal Fluid with Blasts
CRES	CAR-T-cell-related encephalopathy syndrome
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
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CSF	Cerebral Spinal Fluid
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL019 cells	CD 19 Redirected Autologous T cells (previously called CART19 cells)
CVVHD	Continuous Veno-Venous Hemodialysis
DIC	Disseminated Intravascular Coagulation
DOR	Duration of Remission
DLBCL	Diffuse large B-cell lymphoma
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EC	European Commission

ECG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	EthyleneDiamineTetraAceticAcid
EEA	European Economic Area
EEG	Electroencephalography
EFS	Event-Free Survival
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FC	Fludarabine-Cyclophosphamide
FDA	Food and Drug Administration
FISH	Fluorescent *In Situ* Hybridization
FL	Follicular Lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GDPR	General Data Protection Regulation
GGT	Gamma-Glutamyltransferase
GVHD	Graft-Versus-Host Disease
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HHV6	Human Herpes Virus 6
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFNg	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin
IL-6	Interleukin-6
IL-7	Interleukin-7
IL-15	Interleukin-15
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	Idiopathic thrombocytopenic purpura
IUD	Intrauterine Device
IUS	Intrauterine System
IWRS	Interactive Web Response System
IV	Intravenous(ly)

JC	John Cunningham
KM	Kaplan-Meier
LFT	Liver Function Test
LP	Lumbar Puncture
LTFU	Long-Term Follow-Up
LVEF	Left Ventricular Ejection Fraction
LVSF	Left Ventricular Shortening Fraction
MAS	Macrophage Activation Syndrome
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MMc	Maternal Microchimerism
MRA	Magnetic Resonance Angiography
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
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
NR	No Response
NYHA	New York Heart Association
OOS	Out of Specification
ORR	Overall Remission Rate
OS	Overall Survival
PAS	Pharmacokinetic/Cellular Kinetic Analysis Set
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
pH	Hydrogen Ion Concentration; a Measure of the Acidity or Basicity of an Aqueous Solution
Ph+	Philadelphia Chromosome Positive
PHI	Protected Health Information
PML	Progressive Multifocal Leukoencephalopathy
PPS	Per-Protocol Set
PT	Preferred Term
QA	Quality Assurance
q-PCR	Quantitative Polymerase Chain Reaction
RBC	Red Blood Cell
RCL	Replication Competent Lentivirus
REB	Research Ethics Board
RFS	Relapse-Free Survival
r/r	Relapsed/Refractory
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
scFv	Single Chain Variable Fragment of an Antibody
SCT	Stem Cell Transplantation

sIg	Surface Immunoglobulin
SMQ	Standardized MedDRA query
SOC	System Organ Class
TBL	Total Bilirubin
TKI	Tyrosine Kinase Inhibitor
T_{max}	Time to peak concentration
TNF	Tumor Necrosis Factor
TLS	Tumor Lysis Syndrome
TCR	T-cell Receptor
TCR-ζ/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
VASST	Vasopressin and Septic Shock Trial
VSV-g	Vesicular Stomatitis Virus, Glycoprotein
WBC	White Blood Cell

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Dose level	The dose of treatment 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.
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment.
Patient number	A unique identifying number assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as Screening, baseline, titration, washout, etc.
Personal data:	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival.
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	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.

Amendment 4 (06-Aug-2019)

At the time of this protocol amendment, 11 sites have been initiated in Europe (8 sites), Canada (2 sites), and Japan (1 site); 71 patients have been enrolled and 64 patients infused. Enrollment is now closed in France, Germany and Spain.

The protocol is being amended mainly to:

- Include further details on the requirements for leukapheresis due to the fact that the separate leukapheresis study (CCTL019B2206) is now completing and the leukapheresis procedure will be incorporated in this study (i.e. CCTL019B2001X).
- Update the cytokine release syndrome (CRS) treatment algorithm to align with the approved algorithm in the Summary of Product Characteristics (SmPC) including permission of up to 4 doses of tocilizumab in addition to moving siltuximab under alternative measures (as footnote).
- To delete the Japan-specific CRS treatment algorithm as the updated CRS treatment algorithm now covers all possible treatment scenarios for all countries.
- To clarify the rationale for information provided on the approach for out of specification (OOS) CTL019.
- To clarify SAE reporting requirements for grade ≥ 4 neurotoxicities and deaths.
- To increase the projected number of patients from approximately 70 to approximately 80 patients (see below for rationale).
- To remove inclusion criterion no. 4 to align with the approved label in all regions.
- To amend inclusion criterion no. 11 to add note about prohibited concomitant medications and washout times.
- To add new inclusion criterion (no. 12, formerly covered in part by exclusion criterion no. 10) describing inclusion of patients with active CNS leukemia involvement in alignment with the latest amendment of the inclusion and exclusion criteria in CCTL019B2205J (ENSIGN). CNS-3 patients as defined by CSF involvement only at the time of Screening, with CNS-1 or CNS-2 status documented prior to CTL019 infusion, are now eligible based on acceptable safety data from CHP959 (Talekar et al 2017). This population is expected to behave similarly as non-CNS-3 patients, thus it is not anticipated that including patients with CNS-3 by CSF findings will impact the efficacy analysis. Therefore, patients with CNS-3 by CSF findings will be analyzed together with non-CNS-3 patients in the main analysis.
- To amend exclusion criterion no. 7, no. 10 (formerly no. 11), no. 18 (formerly no. 19), and no. 20 (formerly no. 19) for clarity, and to delete exclusion criterion on CNS involvement (formerly no. 10, now covered under inclusion criterion no. 12).
- To update background details on the clinical efficacy and safety of CTL019.
- To update background details and guidance on the management of potential and identified safety risks.
- To update pregnancy reporting details.
- To update serology test requirements.

- To reduce the frequency of laboratory assessments.

The **rationale for increasing the projected number of patients** is as follows:

- In addition to collecting data on safety, efficacy and subgroups that were not included in the pivotal clinical trial (such as age < 3 years and prior blinatumomab exposure), B2001X is a Phase IIIB trial to provide access to eligible patients in countries/regions, where regulatory approval for CTL019 for the treatment of r/r B-cell ALL is not yet obtained, commercial access and/or reimbursement are not yet established following regulatory approval, or for patients who do not meet the approved label indication (e.g. patients < 3 years in Canada).
- Although Kymriah has been approved for r/r in pediatric/young adult patients with B-ALL in Europe by the European Commission in August 2018, and in Canada by Health Canada in September 2018, Kymriah is not marketed and/or reimbursed in all European countries or Canada.
- Study B2001X will still serve as the pathway to provide access to patients, since Kymriah has not been marketed yet in all countries and the timelines to establish reimbursement are variable and lengthy. In Amendment 3 the number of targeted patients was increased from 55 to 70. In Amendment 4 (current amendment), Novartis has further increase the number of targeted patients to approximately 80, in response to the continued investigators' demand to treat eligible pediatric/young adult B-ALL patients within study B2001X.

Further clarification on the **rationale in Protocol Amendment 3 for including patients less than 3 years of age (i.e. removal of lower age restriction)** in this study is provided as follows:

- In CCTL019B2202 (ELIANA) and CCTL019B2205J (ENSIGN) clinical trials for pediatric/young adult patients with r/r B-ALL, the lower age limit of 3 years at the time of screening was based on early experience with the manufacture of CTL019 at the time of study initiation.
- In Study CCTL019B2101J in r/r pediatric B-cell ALL patients at the Children's Hospital of Philadelphia (CHOP) under the sponsorship of the University of Pennsylvania, test expansions of autologous T cells, conducted prior to manufacture of CTL019, from very young patients treated with standard chemotherapy regimen failed to grow in a test expansion *in vitro* and thus, did not qualify for manufacturing. Consequently, pediatric patients below the age of 3 years were not included in the multi-center studies with CTL019. Of note, one 12-month-old patient was treated in the study and achieved complete remission with incomplete count recovery at 4 weeks following infusion.
- Since initiation of the pivotal program at Novartis, improvements and modifications to the Novartis' manufacturing process of CTL019 were implemented.
- FDA and EMA approval of CTL019 in pediatric/young adult patients with r/r B-ALL did not restrict the lower age limit allowing patients up to 25 years of age to be treated (including patients less than 3 years old). Therefore, study CCTL019B2001X is amended to align with the approved Kymriah age range in the US and EU to enable treatment of patients younger than 3 years of age, and to collect further safety and efficacy data in this population.

Changes to protocol (Amendment 4)

Changes to specific sections of the protocol (as listed below) 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: amended statement on purpose of study for clarity.
2. Protocol Summary: amended population section to update number of patients to approximately 80 patients and to add statement regarding leukapheresis.
3. Protocol Summary: deleted inclusion criterion no. 4; amended inclusion criterion no. 10 (formerly criterion no. 11) to add note about prohibited concomitant medications and washout times; added inclusion criterion no. 11 describing inclusion of patients with active CNS leukemia involvement.
4. Protocol Summary: amended exclusion criterion no. 7, no. 10 (formerly no. 11), no. 18 (formerly no. 19), and no. 19 (formerly no. 20) for clarity. Deleted exclusion criterion no. 10.
5. Protocol Summary: amended investigational therapy details to update dose ranges to match the current approved product label and to include reference to leukapheresis.
6. Section 1.2.1.2: updated background clinical information.
7. Section 1.2.1.2.1: updated background efficacy information.
8. Section 1.2.1.2.2: updated background safety information.
9. Section 2.2: added reference to leukapheresis.
10. Section 2.2.1: updated rationale for lymphodepletion to include results of ELIANA study.
11. Section 2.3: updated study rationale for dose and regimen selection to include updated clinical pharmacology details.
12. Section 2.3.1: amended dose levels to match approved product label. Also added reference to leukapheresis, and outlined timing of product release.
13. Section 2.3.1.1: added details on provision of OOS product, including rationale for approach to OOS product provision.
14. Section 2.6.1.2.1: updated background details on risk of viral reactivation.
15. Section 2.6.1.3: updated background details on risk of neurological events.
16. Section 2.6.1.7: updated background details on risk of prolonged depletion of normal B cells and agammaglobulinemia including deletion of sub-section on PML, i.e. Section 2.6.1.7.1 in line with CTL019 program template.
17. Section 2.6.1.8: updated background details on risk of hematopoietic cytopenias not resolved by Day 28.
18. Section 2.6.2.1: updated background details on risk of cerebral edema.
19. Section 2.6.2.3: updated background details on risk of new or secondary malignancies.
20. Section 2.6.2.7: updated background details on risk of transmission of infectious agents.

21. Section 2.6.2.8: updated background details on risk of decrease of cell viability due to inappropriate handling of the product.
22. Section 4.1: added further details on leukapheresis and amended Figure 4-1 to clarify timing of leukapheresis and release of cell product. Updated number of patients.
23. Section 4.1.1: moved contents of Section 4.1.1 to Section 7.1.1.1 for clarity.
24. Section 4.6: removed reference to emergency unblinding as that is not applicable for this open-label study.
25. Section 5.1: updated number of patients and added details on leukapheresis.
26. Section 5.2: deleted inclusion criterion no. 4. Amended inclusion criterion no. 10 (formerly no. 11) to add note about prohibited concomitant medications and washout times. Corrected numbering of criteria 9 and 10. Added inclusion criterion no. 11 describing inclusion of patients with active CNS leukemia involvement at the time of enrollment.
27. Section 5.3: Amended exclusion criterion no. 7, no. 10 (formerly no. 11), no. 18 (formerly no. 19), and no. 19 (formerly no. 20) for clarity. Deleted exclusion criterion no. 10.
28. Section 6.1.1: added reference to leukapheresis and timing of product release.
29. Section 6.1.2: added reference to prohibited medications section.
30. Section 6.1.3: updated wording due to new CRS treatment algorithm, and deleted Japan-specific wording as wording now aligned for all countries.
31. Section 6.1.5: updated language on duration of infusion based on the approved product label.
32. Section 6.1.6: amended allowed dose ranges based on approved product label. Added reference to leukapheresis and timing of product release. Included description of provision of OOS product under exceptional circumstances.
33. Section 6.2.1.1: updated CRS treatment algorithm, which is now covers all countries. Consequently, removed Japan-specific CRS treatment algorithm and associated wording. In addition updated table on high-dose vasopressor use based on the latest literature.
34. Section 6.2.1.2: updated guidance on management of infections.
35. Section 6.2.1.4: updated guidance on management of premedication and hypersensitivity including acute infusion reactions.
36. Section 6.2.1.5: updated guidance on management of tumor lysis syndrome.
37. Section 6.2.1.7: updated section heading on B-cell depletion and/or hypogammaglobulinemia.
38. Section 6.2.1.9: updated guidance on management of RCL.
39. Section 6.2.3: added statement regarding recording of concomitant medications prior to leukapheresis. In addition, amended concomitant medication guidelines for clarity.
40. Section 6.2.4.1: created new sub-section and added statement that medication restrictions before leukapheresis must be followed.
41. Section 6.2.4.2: created new sub-section for clarity.

42. Section 6.5: added details regarding manufacturing of CTL019.
43. Section 7.1: amended study schedule (i.e. Table 7-1) to include leukapheresis at Screening, and to reduce the frequency of the following laboratory assessments: hematology, chemistry, serum Ig levels, urinalysis, and immunogenicity assessments.
44. Section 7.1.1: added statement regarding timing of serum pregnancy assessment prior to leukapheresis.
45. Section 7.1.1.1: created new sub-section on leukapheresis assessment requirements.
46. Section 7.1.1.2: added reference to leukapheresis and timing of product release. Also, updated number of patients.
47. Section 7.1.1.3: added that leukapheresis collection information should be collected for screen failure patients.
48. Section 7.1.2: amended Level 4 subsection headings to spell out timing of study visit days and weeks for clarity.
49. Section 7.1.3.1: deleted urinalysis assessment.
50. Section 7.1.3.2 and relevant subsections: reduced frequency of laboratory assessments in line with Table 7-1.
51. Section 7.1.3.4 and relevant subsections: reduced frequency of laboratory assessments in line with Table 7-1.
52. Section 7.2.2.6: updated requirements for reporting on pregnancy.
53. Section 7.2.3: amended to reduce the frequency of immunogenicity assessments and to adjust the visit window for Day -1.
54. Section 8.1.3: clarified SAE reporting requirements for grade ≥ 4 neurotoxicities and deaths.
55. Section 10.5.4: updated statement to remove reference to reinfusion.
56. Section 10.7: updated number of patients.
57. Appendix 2: updated serology test details.
58. Throughout document as applicable: amended cross reference from “Investigator’s Brochure” to “Investigator’s Brochure, current version”.

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 herein affect the informed consent forms (ICFs) for this study. Sites are required to update and submit for approval revised ICFs that take into account the changes described in this amended protocol.

Amendment 3 (02-Oct-2018)

At the time of this protocol amendment, 11 sites have been initiated in Europe, Canada, and Japan; 50 patients have been enrolled and 37 patients infused. The protocol is being amended for the following reasons:

- To amend age inclusion criterion (no.6) to remove the lower age limit of ≥ 3 years old at the time of Screening and to limit the upper age limit to < 26 years at Screening in line with the authorized product label for tisagenlecleucel for pediatric and young adult patients with r/r B-cell ALL in the United States (approved 30-Aug-2017) and Europe (23-Aug-2018). A positive benefit risk profile has been defined for patients < 26 years of age through the global pivotal study CCTL019B2202 and supportive multicenter study CCTL019B2205. The lower age limit of 3 years in the global pivotal study CCTL019B2202 and supportive multicenter study CCTL019B2205 was originally based on limited experience with the manufacture of CTL019 at the time of study initiation. Early experience at the Children's Hospital of Philadelphia (Study B2101J or CHP959) with test expansion of autologous T cells from very young patients with r/r ALL treated with standard chemotherapy regimen had failed to grow *in vitro* and thus did not qualify for manufacturing at the University of Pennsylvania. With implemented improvements and modifications to the Novartis manufacturing of CTL019 this limitation has been addressed. Successful manufacturing of CTL019 was demonstrated for at least 2 patients < 3 years of age in the commercial setting in the United States post approval, and one 12-month old patient in B2201J study. Consequently, Novartis is not maintaining the lower age limit in pediatric clinical trials. The safety and efficacy of adult patients with r/r B-cell ALL will be investigated in a separate protocol.
- To amend inclusion criterion (no.1) to revise the timing of CTL019 infusion afterallogenic stem cell transplantation (SCT) from ≥ 6 months to ≥ 4 months, and to add the timing of leukapheresis for CTL019 manufacturing to be performed at least 12 weeks following allogenic SCT. This is in line with the authorized product label for CTL019 for pediatric and young adult patients with r/r B-cell ALL in Europe (23-Aug-2018).
- To amend hepatic function inclusion criterion (no.3) to add aspartate aminotransferase (AST) upper limit, and to add exception for patients with Gilbert's syndrome.
- To amend serology exclusion criteria (no. 7 and no. 8) to clarify that testing must be repeated if the interval between Screening and infusion is greater than 8 weeks.
- To amend cardiology exclusion criterion (no. 14) to elaborate on specific types of cardiac abnormalities excluded.
- To amend pregnancy exclusion criterion (no. 17) to clarify that serum pregnancy test is required prior to infusion, and to re-order (no. 18) so it is next to contraception criterion.
- To amend contraception exclusion criterion (no. 19) to indicate requirement for use of highly effective methods of contraception as opposed to effective methods, and to present male contraception requirements as a separate new exclusion criterion (no. 20).
- To remove analysis of adverse events of special interest (AESIs) as AESIs are not part of the study objectives for this Phase 3b study. All AEs will be collected and reported in accordance with the clinical development program for CTL019. Therefore, removing the terminology/text related to AESIs does not exclude events from overall AE reporting.
- To increase the projected no. of enrolled patients from approximately 55 patients to approximately 70 patients based on the current recruitment rate.

- To amend relevant wording on patient withdrawal to reflect the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements.
- To describe guidance for handling of patients undergoing a repeat manufacture of CTL019 cells in case of initial manufacture failure.
- To amend censoring reason for new anticancer therapy to allow for reinfusion of CTL019.
- To update the protocol where required in order to align language with the CTL019 program at the current stage of development. This includes a comprehensive update to the risk/benefit section including potential and identified risks associated with CTL019 treatment, restructuring of guidance for management of AEs, as well as removal of specific analysis of AESIs so safety reporting is aligned with the current clinical development program for CTL019.

Changes to protocol

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

1. Abbreviations: updated list.
2. Glossary: added definition of the terms “personal data” and “withdrawal of informed consent”.
3. Protocol Summary: updated projected number of enrolled patients.
4. Protocol Summary: amended study population age criteria.
5. Protocol Summary: amended inclusion criterion no. 1, no. 3 and no. 6.
6. Protocol Summary: amended exclusion criterion no. 7, no. 8, no. 14, no. 17 (now no. 18 due to re-ordering of criteria) and no. 19, and added exclusion criterion no. 20.
7. Protocol Summary: amended safety assessments to remove reference to AESIs.
8. Section 1.2.1: updated paragraph regarding approval status of CTL019.
9. Section 1.2.1.2: updated clinical experience with CTL019, removing redundant paragraphs.
10. Section 2.1: added paragraph regarding approval status of CTL019.
11. Section 2.6: expanded risk/benefit section on CTL019, including further detail on potential, identified and other risks.
12. Section 4.1: updated projected number of enrolled patients and removed reference to assessment of AESIs.
13. Section 4.4: added section on withdrawal of informed consent to reflect the EEA GDPR requirements.
14. Section 4.5: moved criteria for stopping or pausing the study to this new section for clarity.
15. Section 4.6: added section on discontinuation of study treatment.
16. Section 5.1: amended projected number of enrolled patients and the age criteria for the study population.

17. Section 5.2: amended inclusion criterion no. 1 (bone marrow relapse criterion), inclusion criterion no. 3 (hepatic function criterion) and inclusion criterion no. 6 (age criterion).
18. Section 5.3: amended exclusion criterion no. 7 (hepatitis B and C criterion), exclusion criterion no. 8 (HIV criterion), exclusion criterion no. 14 (cardiac criterion), exclusion no. 17 (pregnancy criterion, which is now exclusion criterion no. 18), exclusion criterion no. 19 (contraception criterion), and created exclusion criterion no. 20 (male contraception criterion).
19. Section 6.1.2: updated pre-infusion evaluation.
20. Section 6.1.3: updated safety procedures prior to CTL019 infusion.
21. Section 6.1.4: updated additional study treatments.
22. Section 6.1.5: added time period for infusion.
23. Section 6.1.6: added guidance for CTL019 dosing in case of out of specification results.
24. Section 6.2.1: updated recommended treatment of adverse events.
25. Section 6.2.3: updated wording on concomitant medications.
26. Section 6.2.4: updated wording on prohibited medications and non-drug therapies.
27. Section 6.3.2: updated wording on potential drug-induced liver injury cases.
28. Section 7.1: updated frequency of assessments for pregnancy testing and pregnancy and menstrual status, as well as urinalyses in Table 7-1 and relevant sub-sections.
29. Section 7.1.1: added check of pregnancy and menstrual status to Screening assessments.
30. Section 7.1.1.1: added guidance for handling of patients undergoing a repeat manufacture of CTL019 cells in case of initial manufacture failure, and amended projected number of enrolled patients.
31. Section 7.1.2.1: added serum pregnancy test at enrollment/pre-chemotherapy evaluation visit.
32. Section 7.1.2.2: added serum pregnancy test and check of pregnancy and menstrual status at the lymphodepleting chemotherapy visit.
33. Section 7.1.2.3: added check of pregnancy and menstrual status, and amended urine pregnancy test to serum pregnancy test at the pre-infusion visit.
34. Section 7.1.3.1: added urinalysis, urine pregnancy test, and check of pregnancy and menstrual status at the infusion visit.
35. Section 7.1.3.2: added urinalysis and check of pregnancy and menstrual status at the Day 2 visit.
36. Section 7.1.3.2.2: added urinalysis and check of pregnancy and menstrual status at the Day 4 visit.
37. Section 7.1.3.2.3: added urinalysis and check of pregnancy and menstrual status at the Day 7 visit.
38. Section 7.1.3.2.4: added check of pregnancy and menstrual status at Day 11.
39. Section 7.1.3.2.5: added urinalysis and check of pregnancy and menstrual status at Day 14.

40. Section 7.1.3.3: added urine pregnancy test and check of pregnancy and menstrual status at Day 28.
41. Section 7.1.3.4.1: added urine pregnancy test at Month 2.
42. Section 7.1.3.4.2: added urine pregnancy test at Month 3.
43. Section 7.1.3.4.3: added urine pregnancy test at Month 4.
44. Section 7.1.3.4.4: added urine pregnancy test at Month 5.
45. Section 7.1.3.4.5: added urine pregnancy test at Month 6.
46. Section 7.1.3.5: added urine pregnancy test at Month 9 and provision of urine pregnancy test kits at Month 9 to cover pregnancy tests at Month 10 and Month 11.
47. Section 7.1.4: added serum pregnancy test at Month 12/End of Treatment.
48. Section 7.2.2: updated frequency of female patient reproductive status checks.
49. Section 7.2.3: updated footnote in Table 7-8 for clarity.
50. Section 7.2.2.5: added section describing ECG assessment.
51. Section 7.2.2.6: moved pregnancy details originally in Section 8.4 to this section.
52. Section 8 and sub-sections: updated safety reporting wording for consistency with current CTL019 development program.
53. Section 10.4: removed reference to AESI assessment.
54. Section 10.4.1: removed reference to AESI assessment.
55. Section 10.4.2.1: removed description of AESI assessment.
56. Section 10.4.5.1: removed description of AESI assessment.
57. Section 10.5.4 and Section 10.5.5: amended censoring reason for new anticancer therapy to allow for reinfusion of CTL019.
58. Section 10.7: updated projected number of enrolled patients.
59. Section 13: updated list of references.
60. Section 14: amended appendices to update Appendix 2 (eligibility based on serology markers) and Appendix 3 (adverse event reporting), and add Appendix 6 (liver event criteria) and Appendix 7 (renal alert criteria).

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 herein affect the informed consent forms (ICFs) for this study. Sites are required to update and submit for approval revised ICFs that take into account the changes described in this amended protocol.

Amendment 2 (09-Jan-2018)

At the time of this protocol amendment, 9 sites have been initiated in Europe and Canada, 15 patients have been enrolled and 7 patients infused. The protocol is being amended to institute updates to allow enrollment of patients previously treated with blinatumomab. Pre-treatment with blinatumomab is being allowed as this is the only other CD19-targeted therapy approved for the population of patients being assessed in this study.

Blincyto® (blinatumomab) was approved on 01-Sep-2016 by the United States (US) Food and Drug Administration (FDA) in pediatric relapsed or refractory Philadelphia negative (Ph-) B-cell ALL. In Jul-2017, the US FDA granted regular approval to blinatumomab and expanded the indication to include Philadelphia chromosome-positive B-cell precursor ALL in adults and children. Prior to this protocol amendment, patients with prior blinatumomab were excluded from this study.

In this protocol amendment, patients who have been previously treated with blinatumomab will only be considered for the study if they have detectable leukemia and documented CD19+ expression (assessed by flow cytometry) with confirmed absence of CD19- leukemic blasts. Those patients who are MRD negative (i.e. leukemic blasts < 0.01%) will be excluded from the study.

For patients who fulfill the specified conditions for entry following blinatumomab, a washout period of at least 1 week between completion of blinatumomab therapy and start of leukapheresis will be implemented, which is considered adequate based on the short half-life of blinatumomab, i.e. half-life of 2.11 ± 4.2 hours (see Blincyto® USPI). This is in addition to the requirement for lymphocytes recovery (ALC and/or CD3+ count) to meet pre-collection criteria already specified in the original protocol.

Furthermore, blinatumomab will not be allowed to be administered as a bridging therapy prior to CTL019 infusion while the patient is awaiting manufacture of CTL019. This is in order to minimize the potential risk of antigen escape and CD19-negative clone selection associated with CD19-directed therapies; and to avoid overlapping toxicity including CRS and neurological toxicities (von Stackelberg et al 2016).

Another change to the protocol is the addition of a statement on the approval of CTL019 (under the tradename Kymriah™) by the US FDA on 30-Aug-2017 for the treatment of pediatric and young adult patients with B-cell precursor relapsed/refractory ALL.

A further change to the protocol is the removal of a reference to the Clinical Overview for CTL019 given the referenced document was submitted to the FDA only and does not apply to the present submission.

The wording of the dose for patients whose body weight is > 50 kg was corrected in Section 2.3.1 and Section 10.1.6. The target dose for patients above 50 kg body weight has not changed and was correctly reflected in Section 6.1 ‘Study treatment’ of the protocol.

Changes to Protocol

Changes to specific sections of the protocol (as listed below) 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: amended inclusion criterion no. 2 and added new inclusion criterion (now inclusion criterion no. 8), and amended exclusion criterion no. 6.
2. Section 1.2.1: Added statement about approval of CTL019 by the US FDA.
3. Section 1.2.1.2: Added cut-off date for number of enrolled patients.
4. Section 1.2.1.2.2: Removed reference to "Clinical Overview for CTL019."
5. Section 2.2: Added background details on blinatumomab.
6. Section 2.3.1: Correction of wording on dosing of patients whose body weight is > 50 kg.
7. Section 4.1.1: Added statement regarding washout period for patients previously treated with blinatumomab in line with inclusion criterion no. 8. In addition, added statement that blinatumomab must not be administered as a bridging therapy prior to CTL019 infusion.
8. Section 4.2: Added estimated end of study date.
9. Section 5.2: Amended inclusion criterion no. 2, added new inclusion criterion (now inclusion criterion no. 8).
10. Section 5.3: Amended exclusion criterion no. 6.
11. Section 7.1, Table 7-1: Added CD19 assessment for patients previously treated with blinatumomab to the Pre-chemotherapy visit, along with clarifying notes.
12. Section 7.1.1: Added statement that blinatumomab must not be administered as a bridging therapy prior to CTL019 infusion. Also added details regarding CD19 assessment for patients previously treated with blinatumomab. Furthermore, added "T-cells" to flow cytometry assessments of peripheral blood.
13. Section 7.1.2.1: Added details regarding mandatory CD19 assessment for patients previously treated with blinatumomab.
14. Section 7.2.1, Table 7-2: Added "T-cells" under flow cytometry assessments of peripheral blood.
15. Section 10.1.6: Correction of wording on dosing of patients whose body weight is > 50 kg.
16. Section 13: Updated list of references.
17. Section 14.1.2.1.4: Deleted redundant statement.

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 herein affect the informed consent forms (ICFs) for this study. Sites are required to update and submit for approval revised ICFs that take into account the changes described in this amended protocol.

Amendment 1 (18-Sep-2017)

Amendment rationale

At the time of this protocol amendment, 2 sites have been initiated and 1 patient has been enrolled. The protocol has been amended mainly to change the study designation from a Phase II expanded treatment program to a Phase IIIb interventional clinical study protocol, to clarify how cytokine release syndrome (CRS) should be managed in Japan, and to update various sections of the protocol to align with the clinical development program for CTL019.

The study designation has been amended from an expanded treatment program to an interventional clinical study protocol in order to align with Novartis protocol procedures given this study includes efficacy assessments in addition to safety assessments. The study phase has been amended from Phase II to Phase IIIb in order to reflect the correct stage of clinical development. While tocilizumab is available in Japan, siltuximab or other alternative anti-interleukin 6 (IL-6) 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 3 doses) along with steroids and with avoidance of tumor necrosis factor (TNF) antagonists. The Japan CRS algorithm now establishes 6 lines of management including required third line steroid treatment, 3 doses of tocilizumab and the avoidance of TNF antagonists. Therefore, the Japan CRS algorithm provides adequate management and guidelines for CTL019-related CRS.

The requirement for reporting of the following serious adverse events (SAEs) in an expedited manner has been removed: any SAE related to a program 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; and deaths attributed to CTL019 occurring 30 days post CTL019 infusion. This wording has been removed as there is no requirement for expedited reporting of these data for this Phase IIIb study at this later stage of the relapsed/refractory (r/r) pediatric ALL program. The reporting requirements for SAEs in this study remain in line with the [Investigator's Brochure]. The following main updates have also been made:

- Safety and efficacy background information has been updated.
- Contraception language has been updated.
- Additional exclusion criteria have been introduced.
- Details regarding the management of toxicities have been updated.
- The standardized process for identification, monitoring and evaluation of liver events has been added for consistency across the CTL019 program.
- Reference to Steering Committee has been removed as there will be no Steering Committee involved in this study.

- Guidelines for use of fibrinogen concentrate in CTL019-associated coagulopathy with hypofibrinogenemia for the EU and Japan have been included in the appendices.

Changes to Protocol

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

1. Title page: Amendment of study type and study development phase.
2. List of abbreviations: Updated.
3. Protocol Summary: Updated exclusion criteria and clarified wording on allowable infused cell dose ranges.
4. Section 1.2.1.2: Updated safety information.
5. Section 1.2.1.2.1: Updated safety information.
6. Section 1.2.1.2.2: Updated efficacy information.
7. Section 2.3.1: Clarified wording on allowable infused cell dose ranges.
8. Section 2.6: Updated risk/benefit.
9. Section 5.3: Updated exclusion criteria.
10. Section 6.1.3: Updated treatment for CRS for Japan only.
11. Section 6.2.4.2.3: Updated CRS section to include number of patients treated with siltuximab in Study CTL019B2202 and to amend the duration of onset of symptoms. Added CRS section for Japan only to address absence of siltuximab in Japan and added Japan CRS management algorithm (Figure 6-2).
12. Section 6.2.4.2.4: Created separate sub-section for neurological events (previously included in Section 6.2.4.2.3 of original protocol).
13. Section 6.2.4.2.6: Updated details on clinical experience of graft-versus-host disease (previously described in Section 6.2.4.2.5 of original protocol).
14. Section 6.2.4.2.7: Updated section on B-cell depletion to include guidance on vaccines.
15. Section 6.2.4.2.8: Added new section on infectious complications, including an update on progressive multifocal leukoencephalopathy (PML) with a diagram on the diagnosis and treatment of PML (Figure 6-3), and an update on hepatitis B reactivation (previously described under Section 6.4.2.3.6 and Section 6.2.4.3.7, respectively, of the original protocol).
16. The following sub-sections, which were included in the original protocol, have been removed and relevant details captured if appropriate under other relevant sub-sections:
    - Section 6.2.4.3.2 (Clonality and insertional oncogenesis) – key aspects now covered under Section 6.2.4.3.2 (New and secondary malignancies).
    - Section 6.2.4.3.3 (Uncontrolled T-cell proliferation) – key aspects now covered under Section 6.2.4.3.2 (New and secondary malignancies).
    - Section 6.2.4.3.4 (Immunogenicity) – immunogenicity testing for this study is still covered in Section 7.2.3 and Section 10.4.2.3.

- Section 6.2.4.3.5 (Immunoglobulin depletion) – key aspects now covered under Section 6.2.4.2.7 (B-cell depletion).
- Section 6.2.4.3.6 (Progressive multifocal leukoencephalopathy, PML) – full details including updates now covered under Section 6.2.4.2.8 (Infectious complications).
- Section 6.2.4.3.7 (Hepatitis B reactivation) – full details including updates now covered under Section 6.2.4.2.8 (Infectious complications).

17. Section 6.2.4.3.2: Updated language on secondary malignancies, including new paragraph on the recording of non T-cell malignancies (previously described in Section 6.2.4.3.8).
18. Section 6.2.4.3.3: Added new sub-section on potential effects on growth and development.
19. Section 6.2.4.3.4: Added new sub-section on new incidence or exacerbation of selected pre-existing conditions.
20. Section 6.2.6: Added cross-reference to new figure (i.e. Figure 6-2).
21. Section 6.3.2.1: Updated section to include standardized process for identification, monitoring and evaluation of liver events.
22. Section 7.1, Table 7-1, and Section 7.1.1, updated cross reference from Section 6.2.4.2.**5** to Section 6.2.4.2.**6** due to section update.
23. Section 7.1.4.1: Updated wording to clarify that a full disease evaluation will be completed for patients who relapse following remission if this is feasible.
24. Section 7.2.3: Added statement to clarify pharmacokinetics and cellular kinetics are used interchangeably.
25. Section 8.1.4: Cross-reference to AESI table corrected from Table 10-3 to Table 10-1.
26. Section 8.2.2: Updated section to remove requirement for expedited reporting of specific SAEs.
27. Section 8.4: Updated details on contraception requirements and added details on potential effects of transduced maternal T cells on pregnancy outcome. Updated follow-up period in case of pregnancy from 6 months to 12 months after birth of baby.
28. Section 10.4.4: Reworded for clarity.
29. Section 11.5: Updated wording on publication of study and results.
30. Section 13: Updated list of references.
31. Section 14 (Appendix 2) - updated eligibility wording in Table 14-4, clarified wording on hepatitis B surface antibody positive finding.
32. Section 14 (Appendix 3) – updated wording on AE/SAE reporting to clarify requirements.
33. Section 14 (Appendix 4) – added guidelines for use of fibrinogen concentrate in CTL019-associated coagulopathy with hypofibrinogenemia for the EU.
34. Section 14 (Appendix 5) – added guidelines for use of fibrinogen concentrate in CTL019-associated coagulopathy with hypofibrinogenemia for Japan.

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 herein affect the informed consent forms (ICFs) for this study. Sites are required to update and submit for approval revised ICFs that take into account the changes described in this amended protocol.

Protocol summary

Protocol number	CCTL019B2001X
Title	Phase IIIb study for relapsed/refractory pediatric/young adult acute lymphoblastic leukemia patients to be treated with CTL019
Brief title	Phase IIIb study for CTL019
Purpose and rationale	The outcome remains poor for pediatric/young adult patients with relapsed/refractory (r/r) 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 (OS) 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 (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. This Phase IIIb study provides pediatric/young adult patients with r/r B-cell ALL the opportunity to be treated with CTL019 after closure of enrollment to the Novartis single-arm phase II pivotal clinical trial (Study CCTL019B2202) until regulatory approval is obtained, commercial product is available, and reimbursement is established in participating countries. This Phase IIIB study will further collect safety and efficacy data, as well as collect data on patient populations that were not included in the pivotal clinical trial such as patients age < 3 years and prior blinatumomab exposure. The enrollment period for this study will continue until enrolment completion of approximately 80 patients or up to the Sponsor's decision to end the trial.
Primary objective	• Evaluate the safety of CTL019 therapy.
Secondary objectives	• Evaluate the efficacy of CTL019 therapy as measured by complete remission (CR) rate, which includes CR and CR with incomplete blood count recovery (CRi). • Evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment. • Evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment. • Evaluate the duration of remission (DOR). • Evaluate the relapse-free survival (RFS). • Evaluate the event-free survival (EFS). • Evaluate the OS. • Evaluate the response at Day 28 ± 4 days. • Evaluate the impact of baseline tumor burden on response. • Evaluate the quality of response using minimal residual disease (MRD) assessments before treatment and at Day 28 ± 4 days after treatment and before SCT by local assessment (flow cytometry +/- quantitative polymerase chain reaction (q-PCR)). • Describe the prevalence and incidence of immunogenicity to CTL019. • Characterize the *in vivo* cellular kinetic profile (expansion, persistence, trafficking) of CTL019 cells in the blood. • Evaluate the relationship between exposure to CTL019 with CRS grades

<table>
<tr><td>Population</td><td>The target population consists of pediatric/young adult patients with B-cell ALL who are chemo-refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT. Approximately 80 patients will be enrolled who are < 26 years of age at the time of Screening. This number of patients is projected based on the availability of eligible patients who have provided acceptable leukapheresis product of non-mobilized cells to the manufacturing site and by the capacity of manufacturing CTL019 product in the Novartis facility at an average of 2 slots per month.All screened patients will undergo non-mobilized leukapheresis for autologous T-cell collection soon after obtaining informed consent.</td></tr>
<tr><td>Inclusion criteria</td><td>The inclusion criteria are as follows:
1. Relapsed or refractory B-cell ALL in pediatric or young adult patients:
a. Second or greater bone marrow relapse, OR
b. Any bone marrow relapse after allogeneic SCT and must be ≥ 4 months from SCT at the time of CTL019 infusion with leukapheresis for CTL019 manufacturing performed at least 12 weeks after allogeneic SCT, OR
c. Primary refractory as defined by not achieving a CR after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukemia, OR
d. Patients with Philadelphia chromosome positive (Ph+) ALL are eligible if they are intolerant to or have failed 2 lines of tyrosine kinase inhibitor (TKI) therapy, or if TKI therapy is contraindicated OR,
e. Ineligible for allogeneic SCT because of:
• Comorbid disease
• Other contraindications to allogeneic SCT conditioning regimen
• Lack of suitable donor
• Prior SCT
• Declines allogeneic SCT as a therapeutic option after documented discussion about the role of SCT with a bone marrow transplantation physician who is not a member of the CTL019 study team.
2. For relapsed patients, CD19 tumor expression demonstrated in bone marrow or peripheral blood by flow cytometry within 3 months of study entry. For relapsed or refractory patients previously treated with blinatumomab, CD19 tumor expression must be demonstrated (via flow cytometry) at Screening.
3. Adequate organ function defined as:
a. Renal function defined as:
• A serum creatinine based on age/gender as follows:
<table>
<tr><th></th><th colspan="2">Maximum serum creatinine (mg/dL)</th></tr>
<tr><th>Age</th><th>Male</th><th>Female</th></tr>
<tr><td>1 to < 2 years</td><td>0.6</td><td>0.6</td></tr>
<tr><td>2 to < 6 years</td><td>0.8</td><td>0.8</td></tr>
<tr><td>6 to < 10 years</td><td>1.0</td><td>1.0</td></tr>
<tr><td>10 to < 13 years</td><td>1.2</td><td>1.2</td></tr>
<tr><td>13 to < 16 years</td><td>1.5</td><td>1.4</td></tr>
<tr><td>≥ 16 years</td><td>1.7</td><td>1.4</td></tr>
</table>
b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 times the upper limit of normal (ULN) for age.
c. Total bilirubin < 2.0 mg/dL (with the exception of patients with Gilbert's syndrome. Patients with Gilbert's syndrome may be included if their total bilirubin is ≤ 4.0 mg/dL).
d. Must have a minimum level of pulmonary reserve defined as ≤ grade 1 dyspnea and pulse oxygenation > 91% on room air.</td></tr>
</table>

	e. Left ventricular shortening fraction (LVSF) ≥ 28% confirmed by echocardiogram (ECHO), or left ventricular ejection fraction (LVEF) ≥ 45% confirmed by ECHO or multiple uptake gated acquisition (MUGA) within 7 days of Screening. 4. Life expectancy > 12 weeks. 5. Age < 26 years of age at the time of Screening. 6. Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50 at Screening. 7. Patients previously treated with blinatumomab who have detectable leukemia and documented CD19+ expression (via flow cytometry) and confirmed absence of CD19- leukemic blasts at Screening may be included. In this case, at least 1-week washout period must be applied from last dose of blinatumomab to start of leukapheresis. Patients previously treated with blinatumomab with no detectable MRD (i.e. MRD negative demonstrated by leukemic blasts < 0.01%) will be excluded. Note: blinatumomab must not be administered as a bridging therapy prior to CTL019 infusion while the patient is awaiting manufacture of CTL019. 8. Signed written informed consent form (ICF) and assent form 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. Note: Please refer to Section 6.2.4 and Section 7.1.1.1 of main protocol for prohibited concomitant medications and washout times to ensure adequate collection as well as the [Investigational Leukapheresis, Cryopreservation and Scheduling Manual] for specific collection procedures. 11. Patients with active CNS leukemia involvement at the time of enrollment defined as CNS-3 by CSF findings only are eligible but will have their CTL019 infusion delayed until CNS disease is reduced to CNS-1 or CNS-2 by CSF findings. Patients with other forms of active CNS-3 leukemic involvement such as CNS parenchymal or ocular disease, cranial nerve involvement or significant leptomeningeal disease are not eligible. However, such patients with other forms of CNS-3 leukemic involvement (non-CSF involvement) are eligible if there is documented evidence of disease stabilization for at least 3 months prior to CTL019 infusion. Patients must have no acute/ongoing neurologic toxicity > Grade 1 with the exception of a history of controlled seizures or fixed neurologic deficits that have been stable/improving over the past 3 months.
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 surface immunoglobulin (sIg) positive and kappa or lambda restricted positivity ALL, with French-American-British Classification System for Hematologic Disease 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. Prior treatment with any gene therapy product. 6. Prior treatment with any anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy, except for patients pre-treated with blinatumomab who fulfill inclusion criterion no. 8.

	7. Presence of active replication of hepatitis B or hepatitis C (for detailed criteria see Appendix 2 of main protocol). Serology must be repeated, if the interval between testing at Screening and CTL019 infusion exceeds 8 weeks. 8. HIV positivity as indicated by serology. Serology must be repeated, if the interval between testing at Screening and CTL019 infusion exceeds 8 weeks. 9. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD). 10. Uncontrolled acute life threatening infection at Screening. 11. Previous or concurrent malignancy with the following exceptions: a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry). b. *In situ* carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study. c. A primary malignancy which has been completely resected and in CR for ≥ 5 years. 12. Intolerance to the excipients of the CTL019 cell product (i.e. dimethyl sulfoxide). 13. Cardiac or cardiac repolarization abnormality, including any of the following: • History of myocardial infarction, angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment. • Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g. bifascicular block, Mobitz type II and third degree AV block). • LVEF <45% as determined by ECHO or magnetic resonance angiography (MRA) or multiple uptake gated acquisition (MUGA). • New York Heart Association (NYHA) functional class III or IV (Chavey et al 2001). 14. Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. 15. Patient has an investigational medicinal product within the last 30 days prior to Screening. 16. 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 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, mycophenolate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-tumor necrosis factor (anti-TNF), anti-interleukin-6 (IL-6) or anti-IL-6 receptor, systemic steroids). d. **Chemotherapy:** • TKIs 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. 17. Pregnant or nursing (lactating) women. **NOTE:** Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours before leukapheresis, lymphodepletion and prior to CTL019 infusion. 18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they agree to using highly effective methods of contraception from enrollment and for at least 12 months after the CTL019 infusion and until CAR T-cells are no longer present by qPCR on 2 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 tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment • Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient • Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 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.

	19. Sexually active males must use a condom during intercourse from enrollment and for at least 12 months after the CTL019 infusion and until CAR T-cells are no longer present by qPCR on 2 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 therapy	Based on the patient's weight reported at the time of leukapheresis/Screening (note: for patients with a historical leukapheresis product, the patient's weight reported at the time of Screening will be used), one of the 2 following allowable dose ranges will be prepared: • For pediatric and young adult patients with r/r ALL whose weight is ≤ 50 kg, the targeted dose is 0.2 to 5.0 × 106 autologous CTL019 transduced viable T cells per kg body weight. • For pediatric and young adult patients with r/r ALL whose weight is > 50 kg, the targeted dose is 0.1 to 2.5 × 108 autologous CTL019 transduced viable T cells.
Safety assessments	Adverse events (AEs), 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. d. Proportion of patients with sustained anti-CTL019 antibody assay titers.
Efficacy assessments	Efficacy will be assessed to adequately evaluate the benefit/risk profile of the treatment. Efficacy of CTL019 therapy as measured by complete remission (CR) rate, which includes CR and CR with incomplete blood count recovery (CRi), which will be determined by assessments of peripheral blood, bone marrow, CNS symptoms, physical examination and cerebral spinal fluid (CSF). The following will also be assessed: • 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 and then proceed to SCT while in remission before Month 6 response assessment. • DOR. • RFS. • EFS. • OS. • Response at Day 28 ± 4 days. • Impact of baseline tumor burden on response. • Quality of response using MRD assessments before treatment and at Day 28 ± 4 days after treatment and before SCT by local assessment (flow cytometry +/- q-PCR).
Cellular kinetic assessments	Cellular kinetic assessments planned for this trial include: • Detection of CTL019 in the blood by q-PCR. • Maximum concentration (C_{max}), time of peak concentration (T_{max}), area under the curve (AUC) and other relevant cellular kinetic parameters of CTL019 in the blood. • Persistence of CTL019 in the blood. • Relationship of C_{max} and $AUC_{0\text{-}28d}$ of CTL019 in the blood with CRS grade.
Key words	CTL019, acute lymphoblastic leukemia, T cells, pediatric/young adult patients

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 most non-Hodgkin's lymphomas. Leukemia is the most common childhood malignancy, accounting for 30% of all cancers diagnosed in children under 15 years of age in industrialized countries. Around 2000, the average incidence for this age group in the European Region was 46.7 cases per million per year, with a slightly lower level in Eastern than in Western European countries (ENHIS Factsheet 2009). There were 66371 lymphoid malignancies registered in 2000-2002 by 44 European cancer registries (Sant et al 2010). The majority of these malignancies were of B-cell origin (Mitchell et al 2012). ALL, which is a malignant proliferation of lymphoid cells blocked at an early stage of differentiation, accounts for 75% of all cases of childhood leukemia. About 3,000 children in the United States and 5000 children in Europe are diagnosed with ALL per year. The peak incidence occurs between 2 and 5 years of age (orpha.net).

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/refractory (r/r) ALL patients (both adult and pediatric patients/young adults) have significant unmet medical needs.

1.2 Introduction to investigational treatment and other study treatment

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-cell lineage ALL (B-cell ALL) has a durable remission rate of less than 10% (Kolb et al 1995), and often at the cost of substantial morbidity due to graft-versus-host disease (GVHD) (Sullivan et al 1989, Appelbaum 2001).

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 major histocompatibility complex (MHC) independent manner (Mellman et al 2011).

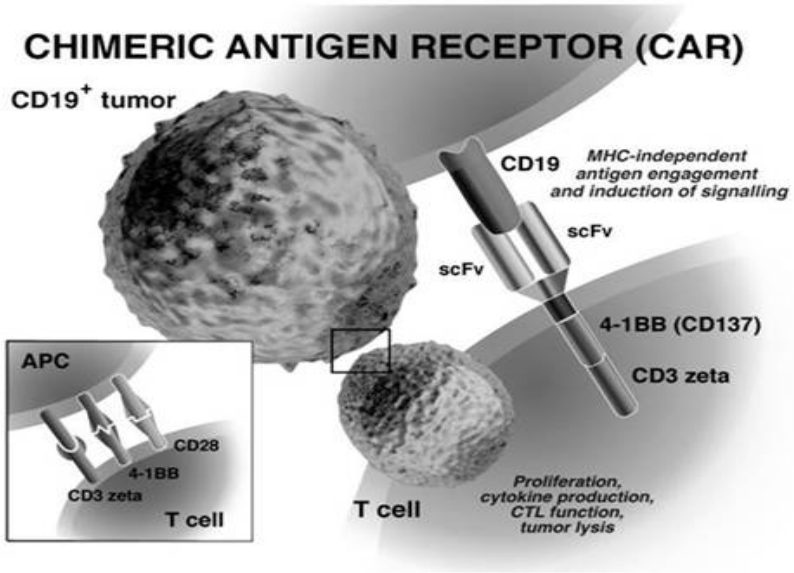
A potential target antigen for B-cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors (Sadelain et al 2003, Brentjens et al 2010, Porter et al 2011). CD19 is not expressed on hematopoietic stem cells or non B-cell tissues. It is a member of the immunoglobulin (Ig) superfamily and a component of a cell surface signal transduction complex that regulates signal transduction through the B-cell receptor (Ledbetter et al 1988, Stamenkovic et al 1988, Fearon et al 2000). Mice lacking CD19 have a decreased number of B cells in peripheral lymphoid tissues, decreased B-cell response to oral vaccines and mitogens, and decreased serum Ig levels (Ledbetter et al 1988, Stamenkovic et al 1988, Tedder et al 1989, Fearon et al 2000).

First generation CARs contain the TCR activation signal domain consisting of TCR-ζ. Second generation CARs contain costimulatory signaling domains as well: either CD28 (i.e. cluster of differentiation 28) or 4-1BB (i.e. type 2 transmembrane glycoprotein belonging to the tumor necrosis factor (TNF) superfamily, expressed on activated T lymphocytes). The third generation CARs contain further advancements such as double costimulatory modules comprised of CD28, 4-1BB, and TCR-ζ (June 2007, June et al 2009, Kohn et al 2011).

CTL019 is an adoptive immunocellular therapy 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 et al 1989, Pinthus et al 2003). These receptors have the ability to recognize intact membrane proteins independent of antigen processing. The tumor antigen binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the heavy chain variable domain and light chain variable domain chains joined by a peptide linker of about 15 residues in length (Mullaney et al 2001).

Early results from ongoing clinical trials of CTL019 in r/r CLL and r/r ALL have shown favorable and durable anti-tumor efficacy (Porter et al 2011, Grupp et al 2013, Maude et al 2014). It is anticipated that CTL019 may offer a therapeutic alternative for patients with r/r B-cell malignancies who are either SCT ineligible or who have relapsed after SCT, which may offer a greater durability of remission than current salvage therapies. In the future, CTL019 may also have the potential to replace 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. CTL019 was approved for the treatment of pediatric and young adult patients with B-cell precursor relapsed/refractory ALL by the US Food and Drug Administration (FDA) on 30-Aug-2017, and by the European Commission (EC) on 23-Aug-2018.

Figure 1-1 CTL019 chimeric antigen receptor design



1.2.1.1 Non-clinical experience

Extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models (Calogero et al 2000, Clay et al 2002, Hombach et al 2002, Pule et al 2003, Sadelain et al 2003). Others have used electroporation or retroviral vectors to create CD19 CAR T cells and have shown in vivo safety and efficacy of adoptively transferred T cells in immunodeficient mouse models (Willemsen et al 2000, Roessig et al 2002, Brentjens et al 2003, Cooper et al 2003, Serrano et al 2006). The incorporation of signaling modules such as CD28 and 4-1BB in second-generation CARs increases the potency of the engineered T cells in pre-clinical studies (Finney et al 1998, Krause et al 1998, Eshhar et al 2001, Maher et al 2002, Finney et al 2004, Friedmann-Morvinski et al 2005, Brentjens et al 2010). The pre-clinical data supporting CAR T-cell persistence, expansion and anti-tumor efficacy have been published (Gross et al 1992, Milone et al 2009).

1.2.1.2 Clinical experience

CTL019 is investigated in several malignancies including relapsed/refractory (r/r) ALL, r/r DLBCL, r/r CLL, and follicular lymphoma (FL). Available data showed encouraging anti-tumor efficacy with manageable toxicity (Grupp et al 2013, Porter et al 2011, Schuster et al 2017, Chong et al 2016, Maude et al 2018). For more details please refer to the [Investigator's Brochure, current edition].

As of 12-Feb-2018, 549 patients have been treated with CTL019 in the clinical development program, including 160 pediatric/young adult patients with r/r B-ALL (75 patients from [Study B2202], 29 patients from [Study B2205J] and 56 patients from [Study B2010J]); and 111 adult patients with r/r diffuse large B-cell lymphoma (DLBCL) [Study C2201] [Developmental Safety Update Report for CTL019].

Clinical cellular kinetics

In adult r/r DLBCL patients from Study C2201, CTL019 typically exhibited an initial rapid expansion phase, achieving maximal expansion around Day 9 followed by a bi-exponential decline. The persistence of CTL019 transgene in peripheral blood has been observed for up to 18 months. All responding patients demonstrated expansion of transgene levels. Neither patient characteristics nor prior therapy had any clinically relevant impact on expansion Cellular and humoral immunogenicity had no impact on the cellular kinetics or clinical outcome (Awasthi et al 2017).

1.2.1.2.1 Efficacy of CTL019

Tisagenlecleucel, also known as 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 2 or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma (Kymriah US PI 2018). 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 2 or more lines of systemic therapy (Kymriah EU SmPC 2018).

Efficacy in r/r pediatric and young adult ALL

The efficacy of CTL019 in patients with r/r pediatric and young adults B-cell ALL (pALL) was evaluated in the pivotal multicenter, single-arm phase II study (CCTL019B2202, ELIANA; Grupp et al 2018, Maude et al 2018). At enrollment, patients had a median age of 11 years, a median of 3 previous therapies (range: 1 to 8); and 46 patients (61%) had undergone previous allogenic HSCT. Of the 97 patients enrolled, 79 patients were infused and evaluable for efficacy. Efficacy was established through the primary endpoint of ORR, which was the sum of proportion of patients who achieved complete remission (CR) or CR with incomplete blood count recovery (CRi), within 3 months post infusion. The ORR was 82% (65/79) (95% CI: 72, 90); CR was achieved in 49 patients (62%) and CRi was achieved in 16 patients (20%). The median DOR was not reached (95% CI: 20 months to NE). The rate of relapse-free survival was 59% at 12 months. The majority of patients did not receive an allogenic stem cell transplant after CTL019. Updated data demonstrated a 24-month overall survival of 66%.

Efficacy in adult r/r NHL

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

In Study A2101J, 14 patients with refractory follicular lymphoma (FL) were infused with CTL019. Ten patients (71%) achieved CR and maintained it for 28.6 months of follow up (Schuster et al 2017).

1.2.1.2.2 Safety of CTL019

Safety in r/r ALL

Cytokine release syndrome (CRS) was observed in 77% (21% Grade 3, 25% Grade 4). The median time to onset of CRS in this population was 3 days after infusion (range: 1 to 22). Neurologic events were reported in 40% of the patients (13% grade 3 and no grade 4). The most common other AEs of any grade were infection (43%), pyrexia (40%), decreased appetite (39%), febrile neutropenia (35%), prolonged cytopenia (not resolved by day 28, 37%) and headache (36%). Tumor lysis syndrome was reported in 4% of patients. A total of 25 post-infusion deaths were reported; 2 deaths occurred within 30 days of infusion and 23 deaths occurred greater than 30 days after infusion (Grupp et al 2018, Maude et al 2018).

Safety in adult r/r B-NHL

In study C2201, among the 111 patients assessed for safety, there were 58% with CRS (14% Grade 3, 8% Grade 4), 21% with neurological events (7% Grade 3, 5% Grade 4), and 34% with infections (18% Grade 3, 2% grade 4). The median time to CRS onset was 3 days (range 1-51 days), median CRS duration was 7 days (range 2-30 days); 15% of patients required tocilizumab and 11% of patients required corticosteroids (Schuster et al 2019).

There were 16 patients who died after CTL019 infusion. Three patients died within 30 days of CTL019 infusion due to DLBCL; 13 patients died more than 30 days (range from 41 to 236 days) after CTL019 infusion (12 due to DLBCL disease progression and 1 due to chronic kidney disease not related to CTL019).

In study A2101J, 28 patients (14 with DLBCL and 14 with FL) were treated with CTL019. Sixteen (57%) patients developed CRS (18% Grade 3-4) and 11 (39%) patients developed neurotoxicity (11% Grade 3-4). There was one death (possibly related to CTL019) in a patient with FL who died 234 days after CTL019 infusion in pathological CR (Schuster et al 2017).

For further information refer to the [Investigator's Brochure, current edition].

Vector-related safety

To date, no vector-related AEs have been seen associated with higher CTL019 transgene levels of expression or persistence in 3 pediatric patients with r/r ALL and in 4 adult patients with r/r CLL.

Post-infusion monitoring for replication competent lentivirus (RCL) in trials with UPENN manufactured CTL019 therapy has shown no Vesicular Stomatitis Virus, Glycoprotein (VSV-g) by quantitative polymerase chain reaction (q-PCR) detectable in any of the patient samples at time points up to 2 years following infusion (7 patients from UPCC03712 trial; 16 patients form UPCC04409 trial, 11 patients from CHP959 trial).

2 Rationale

2.1 Study rationale and purpose

The outcome remains poor for patients with r/r pediatric/young adult B-cell ALL. Treatment options for r/r B-cell ALL include further treatment with salvage chemotherapy, second allogeneic SCT or supportive care. Therapy in this population is not curative with an overall survival (OS) of 3 to 6 months (Oudot et al 2008, Duval et al 2010, Ko et al 2010, Smith et al 2010, Tallen et al 2010, Martin et al 2012). As an example, clofarabine was approved by the FDA for the treatment of pediatric/young adult patients with r/r ALL after at least 2 prior therapeutic regimens. The ORRs were 30% for ALL and 38% for acute myeloid leukemia in Phase I studies (Jeha et al 2004); 30% (20% CR or CR with incomplete platelet recovery and 10% partial remission) for ALL and 26% for acute myeloid leukemia in Phase II studies (Jeha et al 2006). The median duration of remission (DOR) 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 (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/young adult ALL and in r/r CLL.

As described in Section 1.2.1.2.1, CTL019 (also known as tisagenlecleucel) is approved by the EMA and the FDA (Kymriah US PI 2018) for the treatment of patients up to 25 years of age with r/r B-cell ALL and adult patients with r/r DLBCL. This Phase IIIb study provides pediatric/young adult patients with r/r B-cell ALL the opportunity to be treated with CTL019 after closure of enrollment to the Novartis single-arm Phase II pivotal clinical trial (Study CCTL019B2202 entitled “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”) until regulatory approval is obtained, commercial product is available, and reimbursement is established in participating countries. This Phase IIIb study will further collect safety and efficacy data, as well as collect data on patient populations that were not included in the pivotal clinical trial, such as patients age < 3 years and prior blinatumomab exposure.

2.2 Rationale for the study design

This is a single arm, multi-center Phase IIIb study to determine the safety and efficacy of CTL019 in pediatric/young adult patients with r/r B-cell ALL. After assessment of clinical eligibility and availability of leukapheresis product, patients qualifying for the study will be enrolled and start lymphodepleting chemotherapy as indicated per protocol, followed by infusion of CTL019 transduced cells.

Previous clinical data with CTL019 therapy has been generated using cell product manufactured at the Cell and Vaccine Production Facility at the University of Pennsylvania. The current trial will utilize clinical supply manufactured at the Novartis manufacturing facility in Morris Plains, NJ, USA or at the Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany as European contract manufacturing organization. *In vitro* studies assessing the comparability of the manufactured products have completed prior to initiation of this protocol.

The safety of CTL019 therapy, which is the primary objective of this study, will be assessed using standard safety assessments for ALL as used in the clinical development program for CTL019 (including Study CCTL019B2202).

The efficacy of CTL019 will also be assessed in this study due to the specific characteristics of CTL019 that is manufactured using patients' own cells. Efficacy will be evaluated under the secondary objectives of the study using standard outcome measurements as used in the clinical development program for CTL019 (including Study CCTL019B2202). The resultant efficacy data will serve to support the efficacy data collected to date in the clinical trial program for CTL019.

Enrollment of patients pre-treated with blinatumomab

Protocol Amendment 2 instituted updates to allow enrollment of patients with prior blinatumomab exposure. Pre-treatment with blinatumomab is being allowed as this is the only other CD19-targeted therapy approved for the population of patients being assessed in this study. Blinatumomab is a bispecific T-cell engager antibody construct with dual specificity for CD19 and CD3, simultaneously binding CD3-positive cytotoxic T cells and CD19-positive B cells, resulting in T-cell-mediated serial lysis of normal and malignant B cells. Blinatumomab has a similar mechanism of action to CTL019 in that it targets CD19 antigen and is dependent upon patients' T-cells.

The US FDA granted an accelerated approval to blinatumomab in December 2014 for use in relapsed/refractory B-cell precursor ALL. Blinatumomab is a bispecific T cell engager antibody, approved based on the results of a Phase 2, multicenter, single-arm open-label study of 185 patients with Philadelphia Chromosome negative (Ph-) relapsed or refractory B-cell ALL, with 41.6% of patients achieving complete remission (CR) or complete remission with partial hematologic recovery (CRi) within 2 cycles of treatment. The majority of responses (81%) occurred within the first cycle of treatment. Among patients who achieved CR/CRi, 75.3% of patients achieved no detectable minimal residual disease (MRD) (Topp et al 2015).

In September 2016, the US FDA approved the supplemental Biologics License Application of blinatumomab for the treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. The approval was based on results from Study 205, a phase I/II open-label, multicenter, single-arm trial, which evaluated the efficacy and safety of blinatumomab in pediatric patients with relapsed or refractory B-cell precursor ALL. Among 70 patients (who received the recommended dosage of blinatumomab from the phase I data), 27 (39%; 95% CI, 27% to 51%) achieved CR within the first 2 cycles, 14 (52%) of whom achieved complete MRD response. The most frequent grade ≥ 3 adverse events (AEs) were

anemia (36%), thrombocytopenia (21%), and hypokalemia (17%). Three patients (4%) and 1 patient (1%) had CRS of grade 3 and 4, respectively. Two patients (3%) interrupted treatment after grade 2 seizures (von Stackelberg et al 2016).

In July 2017, the US FDA granted regular approval to blinatumomab and expanded the indication to include Philadelphia chromosome-positive B-cell precursor ALL in adults and children. The regular approval was based on the results of the TOWER study, a randomized, open label, multicenter clinical trial, comparing blinatumomab to standard-of-care chemotherapy (Kantarjian et al 2017). The trial demonstrated a statistically significant improvement in overall survival (OS) for patients treated with blinatumomab compared to those treated with SOC (hazard ratio 0.71; 95% CI: 0.55, 0.93, p=0.012). The estimated median OS was 7.7 months in the blinatumomab arm (95% CI: 5.6, 9.6) and 4.0 months in the SOC arm (95% CI: 2.9, 5.3).

2.2.1 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T-cell proliferation (Dummer et al 2002); one finding showed that naïve 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 et al 1999, Surh et al 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 rationale for improved anti-tumor responses. T cells can undergo up to 7 rounds of cell division after being deprived of contact with antigen presenting cells (Kaech et al 2001, van Stipdonk et al 2001). Lymphodepletion eliminates regulatory T cells and other competing elements of the immune system that act as "cytokine sinks", enhancing the availability of cytokines such as interleukin-7 (IL-7) and interleukin-15 (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 × 2 days) and fludarabine (25 mg/m^2 × 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 et al 2003, Rapoport et al 2005). In this protocol, it is proposed to infuse CTL019 T cells into patients that are rendered lymphopenic as a result of cytotoxic chemotherapy. Recent data indicate 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 the ELIANA study (Maude et al 2018), 72 of 75 patients (96%) received lymphodepleting chemotherapy before the CTL019 infusion. Lymphodepleting chemotherapy was not given at investigator discretion if a patient had leukopenia.

2.3 Study 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 1×10^7 to 1×10^9 CTL019 transduced cells (Milone et al 2009). Please see the [Investigator's Brochure, current edition] for further information on preclinical studies. For safety reasons, initial Phase I cell dosing (e.g. CCTL019B2101J) was divided among 3 split infusions (10%, 30% and 60% of the total cell dose). Of the 26 pediatric ALL patients who had a CR, 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 (e.g. CCTL019B2102J), patients have shown responses after a single infusion or multiple infusions. In the Phase II CLL trial (CCTL019A2201), the dose has been given as a single infusion of 1 to 5×10^7 or 1 to 5×10^8 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 2 doses. In responding CLL patients with CR or lasting PR, the CTL019 transduced cell numbers infused have ranged from 1.4×10^7 to 1.1×10^9 cells.

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 > 10000 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 1, 2 or 3 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 1.1×10^6 to 6.3×10^6 CTL019 cells per kg with an acceptable safety profile. At the lower end of this dose range there is concern that doses less than 2×10^6 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 5×10^8 cells (e.g. 6.8, 7.8 and 9.1×10^8 total CTL019 cells). Since the experience with these higher doses is more limited, a cut-off of 2.5×10^8 cells as a maximum dose, based upon a weight > 50 kg, is proposed. Manufacturing consideration and practicality were also considered in the dosing selection.

Data from Study CCTL019B2202/ELIANA (Maude et al 2018) ongoing CTL019 persistence was observed more than 1 year after infusion in patients with a treatment response. Across a 2-log CTL019 dose range, multi-log expansion occurred, and no relationship between infusion dose and expansion was found. This finding indicates that patients can be effectively treated with CTL019 across a wide dose range without an apparent effect on expansion and response.

Regarding dose-response analyses, clinically meaningful responses to treatment with CTL019 were observed across the dose range. Quartile analysis demonstrated similar response rates

across quartiles. In pediatric and young adult patients with r/r B-ALL, logistic regression analysis demonstrated a slight trend toward a decrease in the probability of response at Day 28 for doses at the lower end of the curve, while the probability plateaued for doses higher than 1.5×10^6 cells/kg in patients ≤ 50 kg and 1.0×10^8 cells in patients > 50 kg (OR [total dose]: 1.56; 95% CI, 1.000-2.424) (Awasthi et al 2018).

Dose-safety analyses showed no impact of dose on neurological toxicities was observed in r/r B-ALL. No impact of dose on CRS grade was observed in r/r B-ALL, although logistic regression weight-adjusted dose analysis showed a slight positive trend in the probability of grade 4 CRS (Awasthi et al 2018).

Therefore, based on these analyses that consider the relationships between dose and exposure, safety and response, a recommended CTL019 cell dose range reported for pediatric and young adult ALL patients ≤ 50 kg is 0.2 to 5.0×10^6 autologous CTL019 transduced viable T cells per kg body weight. For patients > 50 kg, the recommended cell dose range is 0.1 to 2.5×10^8 autologous CTL019 transduced viable T cells.

2.3.1 Allowable infused cell dose range of CTL019 product

Based on the patient's weight reported at the time of leukapheresis/Screening (note: for patients with a historical leukapheresis product, the patient's weight reported at the time of Screening will be used), one of the 2 following allowable dose ranges will be prepared:

- For pediatric and young adult patients with r/r ALL whose weight is ≤ 50 kg, the targeted dose is 0.2 to 5.0×10^6 autologous CTL019 transduced viable T cells per kg body weight.
- For pediatric and young adult patients with r/r ALL whose weight is > 50 kg, the targeted dose is 0.1 to 2.5×10^8 autologous CTL019 transduced viable T cells.

Patients will be infused with the maximum cell dose within these ranges that can be individually manufactured. The CTL019 cell product will be released to the study site approximately 4-6 weeks after manufacturing has commenced, provided all required safety and quality release specifications have been met.

Products falling below the minimum values in the above allowable cell dose ranges will be evaluated for provision to the patient under exceptional circumstances after approval by Health Authorities for infusion.

2.3.1.1 Out of specification (OOS) product provision under exceptional circumstances

Given that CTL019 is an autologous advanced medicinal therapy, the final product may occasionally present with release testing result(s) that is/are out of specification (OOS) to the approved release testing. Where administration of such an OOS batch is requested by the treating physician based on a thorough benefit versus risk assessment, taking into account the alternative options for the patient and the consequences of not receiving CTL019 and administration of the product is considered necessary to avoid an immediate significant hazard to the patient, Novartis may provide the OOS batch upon agreement with the Health Authorities.

Rationale for approach to provision of out of specification (OOS) CTL019

Given the complexity and nature of ATMPs, especially of autologous CAR-T products, cases of OOS cannot be fully excluded. Should a CTL019 batch proves to be OOS, Novartis will conduct a thorough evaluation of the risks pertaining to this particular quality defect and its potential impact on product quality, safety, and efficacy. Novartis may decide to not make an OOS batch available regardless of a request for provision by a physician.

A Novartis risk assessment taking quality, safety and efficacy aspects into consideration will be communicated to the treating physician, to allow the physician to perform an independent evaluation of the benefit versus the risks of treating the patient with this batch. In line with chapter 11.5 of the GMP guidance for ATMPs, provision and administration of the product should only occur to avoid an immediate significant hazard to the life of the patient in the presence of a potentially positive/benefit balance. The physician should consider other alternatives, such as other anti-cancer treatment or repeat leukapheresis for re-manufacturing of a new batch if feasible, taking into account the medical status of the patient and the impact of further delay. However, the physician may request the product to be made available for infusion, if conditions set out in section 11.5 of the GMP guidance for ATMPs are met. The infusion of such a product needs to be carefully considered by the physician and the physician's decision should be made based on the patient's clinical presentation and the benefit-risks anticipated for the respective OOS product.

An informed consent form (ICF) related to this exceptional batch provision and containing information about the specific risk(s) is prepared and submitted to the Ethics Committee according to local requirements for their agreement.

The investigator will discuss with the patient the anticipated benefit-risks of a potential administration of the OOS batch and will document the discussion on the informed consent form.

Upon request for supply of the respective OOS batch by the physician Novartis will provide the benefit versus the risk assessment for provision of an OOS batch to the National Health Authority and will seek agreement for exceptional provision of the concerned batch.

National regulations will be followed as applicable and supply of the batch will only be initiated after endorsement by the National Health Authority. Novartis will inform the regional inspectorate responsible for GMP oversight about the agreement of the exceptional provision of an OOS product by the country HA, and about the manufacturer's intention to exceptionally provide the OOS batch to the physician.

The batch may be made available only if no objections are raised by the Health Authorities or Ethic Committees. The product will be administered to the patient only after signature of the related ICF. All documentation will be archived.

The patients treated with such an OOS product will be followed-up in the core study protocol CCTL019B2001X and thereafter will be offered enrollment into the long-term follow-up study CCTL019A2205B according to the same process as the other treated patients.

Novartis is therefore of the opinion that the protocol should inform the investigator, given the nature of CTL019, that exceptional provision of OOS product can be considered under specific conditions and that their medical assessment would be part of the decision of whether or not to provide the product to the patient contingent on the approval of Health Authorities.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparator drugs

Not applicable.

2.6 Risks and benefits

CTL019 administered to over 549 patients in clinical trials across the dose ranges tested has a well characterized safety profile in pediatric and young adult patients including 160 pediatric and young adult patients with B-cell ALL. Overall, it is anticipated that the benefits of CTL019 therapy, including complete and long-term remissions when compared to the current standards of care, will outweigh the risks in this study

Appropriate eligibility criteria are included in Section 5.2 and Section 5.3 of this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs are provided in Section 6.2.1.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and adherence to the recommendations for the management of AEs known to occur with CTL019 exposure and guidance for the investigators in the [Investigator's Brochure, current edition].

Safety risks that have been identified with the use of CTL019 or are considered potentially associated with CTL019 are briefly outlined below.

2.6.1 Identified safety risks

2.6.1.1 Cytokine release syndrome (CRS)

Cytokine release syndrome is an on-target toxicity that is associated with CTL019 cell expansion, activation and tumor cell killing. It is a result of systemic inflammatory response caused when cytokines are released by activated T-cells, including interferon gamma (IFNg), IL-6 and TNF. Severe and life-threatening events have been observed in patients treated with CTL019. In r/r B-cell ALL, appeared to be related to tumor burden, early CRS onset and early fever onset. In DLBCL, the probability of developing CRS of grade 3 and 4 in severity CRS was increased with high CTL019 dose and exposure. In the majority of cases, CRS occurs within the first 2 weeks post-infusion and shows a wide range of clinical signs and symptoms (Table 2-1). Macrophage activation syndrome (MAS) is also associated with CRS as manifested by liver function test abnormalities, cytopenias, and coagulopathy.

Life-threatening and fatal outcomes associated with CRS and severe concomitant infections have been observed in pediatric and adult patients treated with CTL019.

Table 2-1 Clinical signs and symptoms associated with CRS

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

Source: Lee et al 2014

A therapeutic strategy for the management of CRS is provided in Section 6.2.1.1 that should be followed.

2.6.1.2 Infections

There is an increased risk and severity of infections in patients with longer and more intense immunosuppression. Patients treated with CTL019 are at risk of infection for several reasons:

- Underlying bone marrow disease or dysfunction increases the risk of infections.
- Patient with prolonged and profound immunosuppression are at enhanced risk for more frequent and severe opportunistic infections. This may result from preceding anti-cancer treatment, such as radiation or chemotherapy, and lymphodepleting chemotherapy prior to treatment with CTL019 causing severe neutropenia and/or B-cell depletion from CTL019.
- B-cell depletion is known to be associated with hypo- or agammaglobulinemia that contributes to the risk.

Serious infections were observed in patients after CTL019 infusion, some of which were life-threatening or fatal.

2.6.1.2.1 Viral reactivation

Patients with prior or active hepatitis B virus (HBV) or active hepatitis C virus (HCV) were excluded from clinical studies with tisagenlecleucel, because of the potential risk of viral reactivation and the risk of fulminant hepatitis, hepatic failure and fatal outcome. Human immunodeficiency virus (HIV) positive patients have been also excluded, because of the possible effect on HIV viral suppression.

In addition, there is currently no experience with manufacturing tisagenlecleucel for patients who test positive for HIV, active HBV or HCV. Since the initial approval of tisagenelcelucel, leukapheresis materials from patients with latent/past HBV or past HCV are being accepted for manufacturing if there is no evidence of active infection / active viral replication confirmed with undetectable HBV DNA or HCV RNA in the blood, by nucleic acid testing (NAT).

Patients will be screened for any active HBV, HCV or HIV infection prior to leukapheresis.

Patients with active HBV by serology (or positive HBV by NAT), active HCV (positive HCV RNA by NAT), or positive HIV will not be enrolled in the study; for detailed exclusion criteria see Section 5.2, for serology assessment see Appendix 2.

A therapeutic strategy for the management of infections is provided in Section 6.2.1.2.

2.6.1.3 Neurological adverse reactions

Neurological events, including events indicative of encephalopathy and delirium of non-infectious origin, have been observed in patients following various types of T cell directed therapy including CTL019 and other CAR-T cell therapies of other institutions.

The pathophysiology for neurological events, in particular in case of late events, is not fully understood but is thought to be related to generalized T-cell mediated inflammation rather than direct toxicity of CAR-T-cells on the brain (Tey 2014). Some of the neurological events observed may be related to CRS, but whether this results from systemic cytokines crossing the blood brain barrier and engaging cytokine receptors in the brain or from direct cytokine production in the CNS is not clear (Maus et al 2014). There are no clear predictors of neurologic toxicity. Confounders, such as preceding or newly induced anti-cancer treatment regimens might be involved.

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

In clinical trials, the majority of neurological events following CTL019 infusion were observed within 8 weeks, however, neurological events with later onset > 8 weeks and not in the context of CRS have also been reported. Most neurological events observed within 8 weeks were transient or self-limiting in nature. Frequently, encephalopathy, confusional state and delirium were observed. Other manifestations include a multifarious set of signs and symptoms including seizures, aphasia, speech disorder, and tremor. Some of the events are severe and may have a life-threatening outcome.

Notably, the onset of neurological events can be concurrent with CRS, following resolution of CRS or in the absence of CRS. Onset of neurological events may be concurrent with high fever during the development and at the time of maximal grade of CRS. The incidence appeared to be greater with higher CRS severity and prior history of CNS leukemia and history of other prior CNS diseases. Encephalopathy typically occurred after peak CRS symptoms and tended to be self-limiting with some exceptions. Delayed onset of neurological events may also occur as CRS is resolving or after CRS has completely resolved.

In paediatric and young adult B-cell ALL patients, manifestations of encephalopathy and/or delirium occurred in 40% of patients (13% were Grade 3; no grade 4 were observed) within 8 weeks after tisagenlecleucel infusion. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 21% of patients (12% were Grade 3 or 4) within 8 weeks after CTL019 infusion.

The causality assessment of neurological events in patients treated with CTL019 can be confounded, as CNS toxicity can be associated with chemotherapy used for lymphodepletion and the presence of co-morbid conditions such as CRS, fever and infections.

For the management of neurological events, see Section 6.2.1.3.

2.6.1.4 Hypersensitivity including acute infusion reactions

Biotherapeutics including CAR-T are highly reactive on the immune system, and are often associated with immune mediated hypersensitivity reactions. These reactions can involve a variety of different pathomechanisms, which may resemble those of xenobiotics or characterized by very distinct pathophysiologies. Therefore, to address this, different classifications of hypersensitivity reactions observed with biotherapeutics have been suggested over the past years (Pichler 2006, Sethu et al 2012, Corominas et al 2014).

Although CTL019 is an autologous cellular product, immunogenicity may result from host immune responses against CD19-specific CAR transgene, expressing immunogenic epitopes derived from the murine scFv extracellular binding domain (fused to the intracellular signaling domains of 4-1BB and CD3zeta) or novel epitopes arising at junctions between components of the CAR fusion polypeptide (Park et al 2007, Lamers et al 2006, Lamers et al 2007, Lamers et al 2011).

Hypersensitivity reactions may also occur due to the excipients (such as dimethyl sulfoxide (DMSO) or dextran 40) of the infused solution in which the cells are dispersed. Infusion of DMSO-preserved stem cells into patients can be associated with transient toxic reactions such as nausea, vomiting, cardiac dysfunction, anaphylaxis, acute renal failure, hypotension and hypertension (Bakken 2006).

Clinically, hypersensitivity reactions can be classified as ‘immediate’ or ‘delayed’ depending on their onset after drug administration (Corominas et al 2014, Limsuwan and Demoly 2010). In principle, immediate reactions including acute infusion reactions occur within less than 1 hour after drug administration and may present in a wide range of symptoms such as fever, chills, nausea, urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, bronchospasm, tachycardia, hypotension, anaphylaxis or anaphylactic shock. Delayed hypersensitivity

reactions appear after more than 1 hour and up to several days after drug exposure and could include variable cutaneous symptoms such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, or drug reaction with eosinophilia and systemic symptoms (DRESS) (Averbeck et al 2007, Descotes 2012, Corominas et al 2014, Vultaggio et al 2016).

A therapeutic strategy for the management of hypersensitivity including acute infusion reactions is provided in Section 6.2.1.4.

2.6.1.5 Tumor lysis syndrome (TLS)

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

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

Tumor lysis syndrome was clinically observed in a timely relation to CTL019 T-cell expansion. In the clinical experience with CTL019 thus far, most cases of TLS had a grade 3 in CTCAE severity, however, the risk has been moderate to low with appropriate monitoring after lymphodepleting chemotherapy, prophylaxis and treatment as needed.

A therapeutic strategy for the management of TLS is provided in Section 6.2.1.5.

2.6.1.6 Febrile neutropenia

Febrile neutropenia observed with CTL019 can be caused due to multiple factors, including underlying bone marrow disease, prior chemotherapies, radiation treatments or lymphodepleting chemotherapy, reduced response to growth factors (either exogenous or endogenous) in addition to B cell aplasia that may favor a production of auto-antibodies binding to the neutrophil surface resulting in neutropenia and also disturb the balance between granulopoiesis and lymphopoiesis in the bone marrow (Tesfa and Palmblad 2011).

Febrile neutropenia and associated events such as grade 3 or grade 4 decreased neutrophil counts with elevated temperature were reported in clinical studies with CTL019. The use of chemotherapy is known to be associated with the risk of neutropenia and if severe, with febrile neutropenia. The risk of neutropenia depends on various factors such as type and dose of chemotherapy used, age, gender, performance status and baseline hematology laboratory data. As lymphodepleting therapy is used in all patients with a WBC count >1000 cells/μL, febrile neutropenia is seen in patients treated with CTL019 regimen. Also, as lymphodepleting therapy

is given close to the infusion of CTL019 (within 2 weeks), therefore, overlapping toxicities can be expected.

A therapeutic strategy for the management of febrile neutropenia is provided in Section 6.2.1.6.

2.6.1.7 Prolonged depletion of normal B cells and agammaglobulinemia

B-cell aplasia is an expected on-target toxicity of a successful CD19-directed CAR T cell therapy and a useful surrogate reflecting the persistence of CAR T cells and effectiveness of treatment. B-cell aplasia is observed in all responding patients. The AEs observed after CTL019 infusion were managed well by treatment with immunoglobulins.

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

Given that a typical T-cell may have a lifespan of 40 years, CTL019 may potentially be detectable in a patient for a very prolonged period and prolonged depletion of B-cells may occur, in particular in the subset of patients who continue to demonstrate a tumor response. Long-term data are currently not available.

The AEs observed after CTL019 infusion were managed well by treatment with immunoglobulins. A therapeutic strategy for the management of B cell depletion with resulting hypogammaglobulinemia is provided in Section 6.2.1.7.

2.6.1.8 Hematopoietic cytopenias not resolved by Day 28

Hematopoietic cytopenias are an on-target effect after CTL019 infusion and CTL019 activity also targeting normal B-cells. Prolonged hematocytopenias not resolved by Day 28 are considered a consequence. The etiology of the cytopenias may either be the CAR-T-cell therapy itself or prior anti-cancer treatment, such as chemotherapy (i.e., multiple lines and cycles) or radiation, or lymphodepleting chemotherapy (Brudno and Kochenderfer 2016), exerting cytotoxic effects.

Cytopenias not resolved by Day 28 are commonly seen in patients receiving CTL019. Patients may continue to exhibit cytopenias for several weeks following CTL019 infusion. Prolonged neutropenia has been associated with increased risk of infection. A therapeutic strategy for the management of hematopoietic cytopenias is provided in Section 6.2.1.8.

2.6.2 Potential safety risks

Thus far, an association with the potential safety risks briefly described below and CTL019 have not been confirmed. However, these topics are being closely monitored due to their clinical relevance.

2.6.2.1 Cerebral edema

Fatal cases of cerebral edema, soon after infusion with rapid evolution, have been reported with CAR-T cell therapies other than CTL019; in 5 patients in the Rocket study evaluating JCAR015 for the treatment of ALL and in 1 subject in the Zuma-1 study evaluating KTE-19 for the treatment of CLL (Gilbert 2017, Gust 2017). The patient in the Zuma-1 study is described as becoming febrile on Day 1 and progressing from Grade 3 to Grade 4 CRS, refractory to tocilizumab and dexamethasone, by Day 4. Cerebral edema developed on Day 9, was refractory to siltuximab and mannitol, and led to death on Day 11 (Turtle et al 2017).

No fatal cerebral edemas have been reported following CTL019 infusion in the clinical development program or the post-marketing setting to date that would resemble 5 fatal events reported for JCAR015.

2.6.2.2 Replication competent lentivirus (RCL) production

Replication-competent lentivirus may be generated during CTL019 manufacturing using a lentiviral vector to encode anti-CD19 CAR or subsequently after introduction of vector transduced viable T cells into the patient.

However, an RCL resulting from manufacturing is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL Thus patients will only receive cell products that meet RCL release criteria considered sufficient to confirm the absence of RCL in CTL019 and the negligible probability of *de novo* generation of any RCL.

No AEs related to generation of RCL were noted post-infusion in the CTL019 development program. However, generation of an RCL following CTL019 infusion remains a theoretical possibility. The development of RCL could pose a risk to both the patients and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial (see [Investigational Product Handling Manual] for a description of the assays).

As per guidance for gene therapy medicinal products, patients exposed to CTL019 will be monitored for 15 years following last treatment for vectors persistence and RCL within the long-term follow-up study.

The management of this potential risk is addressed in Section 6.2.1.9.

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

Secondary malignancies in cancer patients, i.e., newly occurring malignancies other than the primary malignancy (e.g., T-cell and non-T-cell hematological malignancies, solid tumors), can be increased as a result of both previous chemotherapy and radiation therapy exposure and partly due to increased rates within families (Friedman et al 2010). The rate of new malignancy detection following CTL019 therapy will need to take into account these additional confounding risk factors.

There is a theoretical concern that transduction of a patient's T-cells with the lentiviral vector could lead to insertional mutagenesis resulting in an uncontrolled T-cell proliferation and an oncogenic effect that could result in a T-cell leukemia or lymphoma and maybe other malignancies. The CTL019 lentiviral vector has been specifically designed to safeguard against the potential oncogenic effects.

CTL019 uses third generation self-inactivating lentiviral vector. Insertional mutagenesis was addressed in 2 lentivirus insertion site analysis (LISA) studies where 12 batches of manufactured patient product ready for infusion and 2 batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration near genes of concern, no preferential sites of integration (hot spots), and no preferential outgrowth of cells harboring integration sites of concern.

CTL019 is based on autologous, fully differentiated T cells and therefore the carcinogenicity risk is considered to be low in comparison to genetic modification or repair such as HSC. In a recent review of CAR-T cell therapies, Bonifant et al (2016) as well as Mohanlal et al (2016) discussed that to date no cases of malignant transformation have been reported for genetic modification of T-cells and that there currently is no evidence for vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation. This is supported by the results of the LISA studies performed during the development of CTL019.

Theoretically, CAR-positive viable T cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies (Milone et al 2009) and clinical experience to date (Porter et al 2011, Grupp et al 2013, Maude et al 2014), CAR-positive viable T cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen. In the context of CTL019 therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be either harmful depending on the extent of proliferation or beneficial, since clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials (Dudley et al 2002, Dudley et al 2005).

The management of this potential risk is addressed in Section 6.2.1.10. All secondary malignancy should be managed/treated according to current medical practice and local standard of care. For the follow-up of secondary malignancy, please see Section 8.2.3.

2.6.2.4 New occurrence or exacerbation of an autoimmune disease

Most autoimmune diseases are driven by a dysfunction in the immune network consisting of B-cells, T-cells, and other immune cells. Reciprocal roles of T-cell help for B-cells during adaptive immune responses and B-cell help in CD4+ T-cell activation are being increasingly recognized (Hampe 2012).

An emerging number and variety of autoimmune diseases following after anti-cancer treatment including immunotherapy are reported, ranging from asymptomatic immunological alterations to life-threatening systemic autoimmune diseases (Pérez-De-Lis et al 2017). However, specific etiopathogenic mechanisms that could clearly link the induced autoimmune disorder with the

immunological pathways altered by the anti-cancer treatments are not well understood. Persistent immune abnormalities after treatment with chemotherapy, development of auto-antibodies and neoantigens are proposed to be crucial in the pathogenesis of autoimmune diseases post anti-cancer treatment (Descotes and Gouraud 2008, Chang and Gershwin 2010, Amos et al 2011).

Based on current knowledge, the risk of autoimmune reaction is considered low with CTL019, since CD19 is not present on most normal tissue other than normal B-cells. The occurrence of new incidence or exacerbation of an autoimmune disorder has not been observed with CTL019 thus far. Prior chemotherapy, radiation or concomitant treatment may also contribute to the risk.

The use of tocilizumab, a monoclonal antibody against the IL-6 receptor, can exacerbate demyelinating autoimmune diseases, and therefore it is to be used with precaution in such conditions (Actemra® USPI). The use of tocilizumab in this study for the management of CRS is described in Section 6.2.1.1.

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

There is potential risk of a hematologic disorder such as myelodysplastic syndrome, aplastic anemia or bone marrow failure given that CTL019 is a genetically modified cell product that may have the potential to affect hematopoietic cell function, as could prior chemotherapy and radiation given for the underlying malignancy.

2.6.2.6 Aggravation of graft versus host disease (GVHD)

The chance of GVHD occurring in patients is low, but it is a potential risk with CTL019 therapy in patients with mixed chimerism of host and donor hematopoietic cells due to prior allogeneic HSCT. A study of activated donor lymphocyte infusions (ex vivo activated cells collected from the donor and grown in the same fashion as 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). Of 18 ALL patients treated with autologous CTL019 therapy who had relapsed after prior allogeneic HSCT with residual mixed chimerism, none have developed GVHD after autologous CTL019 infusion (Maude et al 2014). Long-term data are currently limited.

For the management of GVHD see Section 6.2.1.11.

2.6.2.7 Transmission of infectious agents

There is a potential risk of transmission of infectious agents (that could lead to new infections and reactivation of pre-existing viral disease, e.g. HBV, HCV, or HIV) to close contacts including personnel involved in the CTL019 manufacturing process or health care providers involved in leukapheresis and administering CTL019 or patients treated with CTL019.

Multiple steps are required to produce CTL019 CAR-T-cells, involving leukapheresis to obtain patient autologous starting material, enrichment and activation, gene transduction via lentiviral vector and expansion. Transmission of infections material via product could potentially derive from the patient's own leukapheresis material prepared from autologous blood, other material

including the CTL019 viral vector required to manufacture CTL019, through contamination during the manufacturing process or inadequate storage.

Due to the nature of the product (i.e. cells), there is no possibility to introduce terminal sterilization or dedicated viral removal and inactivation steps. Stringent precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of CTL019 are in place in compliance with principles of good manufacturing practices and regulatory guidelines. The risk associated with CTL019 is considered low.

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

Inappropriate handling of the manufactured product including transport, storage in addition to thawing and standing time prior to infusion may result in a decrease of viable cells. This may impact the efficacy and safety profile of CTL019. Inconsistencies may arise due to product handling including subjective determination of the thaw endpoint and risk of water borne contamination. No AEs indicative of this potential risks were observed in clinical trials to date.

Qualified center personnel must follow appropriate protocols for product handling to receive, thaw, and infuse the finished CTL019 product. Please refer to the [CTL019 Leukapheresis Cryopreservation and Scheduling Manual for Clinical Trials].

2.6.3 Other risks

2.6.3.1 Pregnancy, lactation, and effects on fertility

No preclinical reproductive studies have been conducted with CTL019 to assess whether it can cause fetal harm when administered to a pregnant woman. There is a potential risk that immunologically active maternal CTL019 positive CAR T cells may cross the placenta. The impact on the offspring's B cells is unknown. The survival of normal maternal cells in the fetus is usually limited owing to effective rejection by an immunocompetent target. However, maternal cells can persist in immunocompetent offspring into adult life (maternal microchimerism (MMc)). MMc has been observed in healthy fetus and adults, and was observed in up to 42% of cord blood samples from healthy newborns (Muller et al 2001). The persistence of maternal cells in offspring's tissues and circulation has been associated with autoimmune disorders. The histocompatibility antigens (HLA) disparity between mother and fetus has been hypothesized as responsible for the pathogenesis of some auto-immune diseases.

The testicular environment is usually immunosuppressive to T cells, leading to control and low numbers of T lymphocytes including CD19 CART cells (Hedger and Meinhardt 2000). If transferred to female reproductive tract along with sperm, T cells are likely to be recognized as non-self by the female immune system and therefore be destroyed. A fundamental risk may arise from the presence of RCL the female organism may be exposed to after sexual intercourse. However, the principal design of the vector and the analytic measures taken during manufacturing of CTL019 will exclude the presence of RCL with highest probability, and the female risk for exposure to CTL019 and/or RCL is considered extremely low.

As it is also not known whether CTL019 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, CTL019 should not be administered to pregnant women and care should be taken to avoid conceptions.

Therefore, women of child bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, and sexually active males are excluded from clinical trials with CTL019 unless they use adequate contraception. No data are currently available to determine the duration of contraception after receiving CTL019. Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

There is no information regarding the presence of CTL019 in human milk, the effect on the breast-fed child or the effects of CTL019 on milk production. Nursing women are excluded from participation in this study.

3 Objectives and endpoints

Objectives and related endpoints for the study are described in Table 3-1.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
Evaluate the safety of CTL019 therapy	Type, frequency and severity of adverse events (AEs) and laboratory abnormalities	Refer to Section 10.4.2
Secondary		
• Evaluate the efficacy of CTL019 therapy as measured by complete remission (CR) rate, which includes CR and CR with incomplete blood count recovery (CRi).	CR assessment during the 6 months after CTL019 administration that includes CR + CR with CRi; See Appendix 1 for response definition	Refer to Section 10.5.1
• Evaluate the percentage of patients who achieve CR or CRi at Month 6 without stem cell transplantation (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
• 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 10.5.3
• 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 10.5.4
• 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 10.5.5
• 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 10.5.6
• 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 10.5.7
• 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 10.5.8
• Evaluate the impact of baseline tumor burden on response	Response as a function of baseline tumor burden (tumor load) (minimal residual disease (MRD), extramedullary disease, etc.)	Refer to Section 10.5.9

Objective	Endpoint	Analysis
• Evaluate the quality of response using MRD assessments before treatment and at Day 28 ± 4 days after treatment and before SCT by local assessment (flow cytometry +/- quantitative polymerase chain reaction (q-PCR))	MRD quantitative result (% leukemic cells) and qualitative result (positive/negative)	Refer to Section 10.5.10
• Describe the prevalence and incidence of immunogenicity of antibodies against CTL019	• Prevalence and incidence of immunogenicity and anti-CTL019 assay titers	Refer to Section 10.4.2.3
• Characterize the *in vivo* cellular kinetic profile (expansion, persistence, trafficking) of CTL019 cells in the blood	• Maximum concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC) and other relevant kinetic parameters of CTL019 in the blood • Persistence of CTL019 in the blood	Refer to Section 10.5.12
• Evaluate the relationship between exposure to CTL019 with CRS grades	• Relationship of C_{max} and $AUC_{0\text{-}28d}$ of CTL019 in the blood with CRS grade	Refer to Section 10.5.12

4 Study design

4.1 Description of study design

This single-arm, multi-center Phase IIIb study will provide pediatric/young adult patients with r/r B-cell ALL the opportunity to be treated with CTL019 after the closure of enrollment to the Novartis single-arm Phase II clinical trial (i.e. Study CTL019B2202). The main purpose of this study is to assess the safety of CTL019 for up to 12 months after the CTL019 infusion.

This study will have the following sequential phases for all patients: Screening (Section 7.1.1) including leukapheresis (Section 7.1.1.1), Pre-Treatment (Cell Product Preparation and Lymphodepleting Chemotherapy) (Section 7.1.2), Treatment and Follow-up (Section 7.1.3), and LTFU under a separate protocol (Section 7.1.5) as depicted in Figure 4-1. The enrollment period for this study will continue until enrolment completion of approximately 80 patients or up to the Sponsor's (i.e. Novartis) decision to end the trial. Each enrolled patient will be followed in this study for up to 12 months after the CTL019 infusion, after which time they will be transitioned into the LTFU protocol.

All screened patients will undergo non-mobilized leukapheresis (Section 7.1.1.1) for autologous T-cell collection after obtaining informed consent. Only following confirmation of the patient's eligibility will the leukapheresis product be shipped to the Novartis manufacturing facility. After confirmation of leukapheresis acceptance by Novartis manufacturing, the patient will be enrolled in the trial and will undergo further evaluations required during the pre-infusion phase (Table 7-1). During this time, the patient may also receive bridging therapy and/or lymphodepleting chemotherapy prior to CTL019 infusion (Section 7.1.2.1). After CTL019 infusion, the patient will enter the treatment and follow-up phase and will be followed for safety and efficacy as per Table 7-1.

Safety will be assessed throughout the study via laboratory abnormalities and AE(s)/SAE(s) as described in Section 7.2.2 and Section 7.1.1.

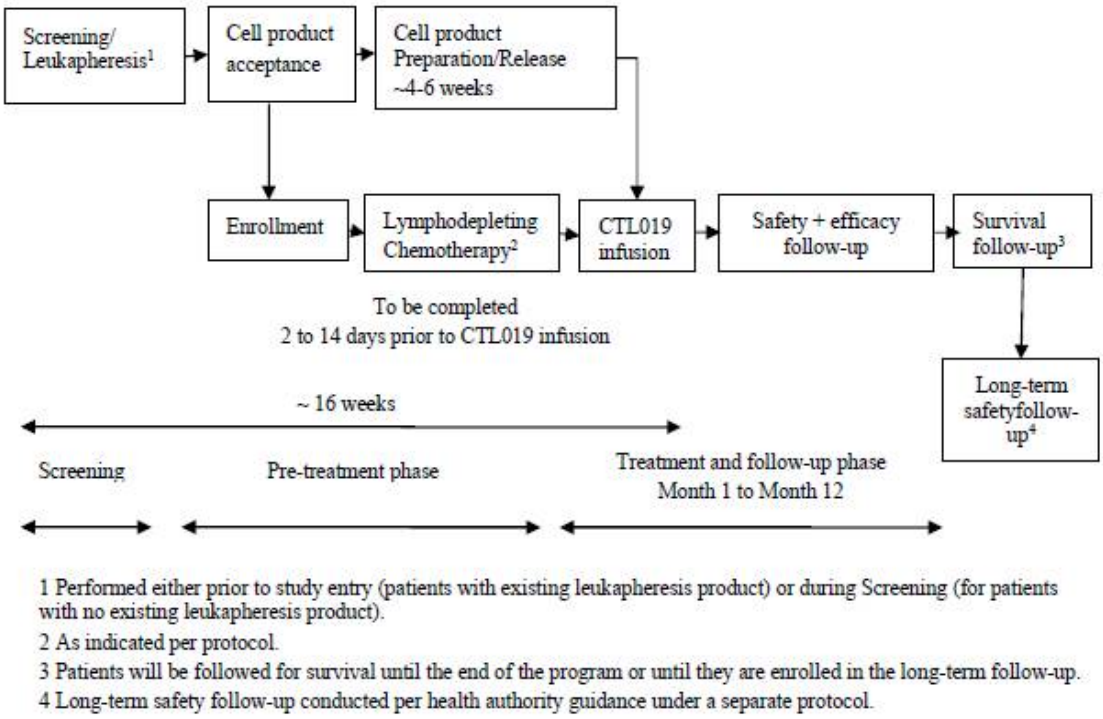
After the CTL019 infusion on Day 1, efficacy will be assessed at Month 1, 3, 6, 9 and 12 or until patient relapse. Efficacy assessments will include assessment of CR rate, DOR, relapse-free survival (RFS), event-free survival (EFS), OS, and MRD as described in Section 7.2.1. Efficacy assessments will be based on the Novartis guidelines for response assessment in ALL (Appendix 1), which is based on National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2017, v1, Cheson et al 2003 and Appelbaum et al 2007).

Cellular kinetic and immunogenicity assessments will also be performed as described in Section 7.2.3, Section 10.4.2.3 and Section 10.5.12.

Patients may be eligible for a second or subsequent infusion of CTL019 as described in Section 6.1.6. In this case, assessments will be repeated as described in Section 7.1.

At the end of this study, patients will be transitioned over to a LTFU study for lentiviral vector safety and efficacy follow-up (Section 7.1.5) that will be run under a separate protocol in accordance with the following health authority guidelines: FDA (2006a), FDA (2006b), European Medicines Agency (EMA) (2008) and EMA (2009).

Figure 4-1 CTL019 in relapse/refractory B-cell pediatric/young adult ALL



1 Performed either prior to study entry (patients with existing leukapheresis product) or during Screening (for patients with no existing leukapheresis product).
2 As indicated per protocol.
3 Patients will be followed for survival until the end of the program or until they are enrolled in the long-term follow-up.
4 Long-term safety follow-up conducted per health authority guidance under a separate protocol.

4.2 Definition of end of the study

The end of study (EOS) is defined as the last patient's last visit, which is the last patient's Month 12 evaluation, or the time of premature withdrawal (see Section 4.3). The EOS is anticipated to occur around Quarter 3, 2020.

Semiannual and annual evaluations will be performed for up to 15 years on all patients under a separate LTFU protocol (i.e. CCTL019A2205B) as recommended by health authority guidance for patients treated with gene therapies. All patients who either complete this study or prematurely discontinue from this study will be enrolled in the LTFU protocol (Section 7.1.5) at the time of study completion/discontinuation (separate informed consent form (ICF)/assent forms will be provided for the LTFU protocol).

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 4.5 are met. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.4 for a prematurely withdrawn patient. The Treating Physician 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. Patients who have received a CTL019 infusion and either discontinue early or complete this study will be transitioned to a LTFU study (i.e. CCTL019A2205B), which will be run under a separate protocol, for follow-up of lentiviral vector safety and efficacy for 15 years post infusion per health authority guidelines. The

Treating Physician will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs)/ Research Ethics Boards (REBs) of the early termination of this study.

4.4 Withdrawal of informed consent

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

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

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table (Table 7-1) and in Section 7.1.4.

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 Europe and Rest of World: 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.

4.5 Criteria for stopping or pausing the study

The 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 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 3 weeks of the CTL019 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, seizure), 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 cardiac dysfunction.
- Death suspected to be related to CTL019 therapy.

4.6 Discontinuation of study treatment

Study treatment (e.g. CTL019 infusion, lymphodepletion, bridging therapy and other therapies used in combination with CTL019) may be discontinued if, in the investigator's opinion, its continuation would be detrimental to the patient's safety.

Patients who discontinue from study treatment and follow-up should NOT be considered withdrawn from the study before they return for the EOT assessments indicated in Section 7.1.4. If they fail to return for these assessments, every effort (e.g. telephone, email, letter) should be made to contact them.

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

Study treatment must be discontinued under the following circumstances:

- Patient/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the patient
- Emergence of the following AEs: Consider any AEs that in the judgment of the investigator, taking into account the patient's overall status, prevent the patient from continuing participation in the study. Any laboratory abnormalities that in the judgment of the investigator, prevents the patient from continuing participation in the study

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

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 4.4). Where possible, they should return for the assessments indicated in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact until the end of the 12-month follow-up period post infusion:

- New / concomitant treatments.
- AEs/SAEs.

5 Population

5.1 Patient population

The target population consists of pediatric/young adult patients with B-cell ALL who are chemo-refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT. Approximately 80 patients will be enrolled who are < 26 years of age at the time of Screening. This number of patients is projected based on the availability of eligible patients who have provided acceptable leukapheresis product of non-mobilized cells to the manufacturing site and by the capacity of manufacturing CTL019 product in the Novartis facility at an average of 2 slots per month. All screened patients will undergo non-mobilized leukapheresis for autologous T-cell collection soon after obtaining informed consent.

The Treating Physician or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in this study.

5.2 Inclusion criteria

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

The inclusion criteria are as follows:

1. Relapsed or refractory B-cell ALL in pediatric or young adult patients:
    a. Second or greater bone marrow relapse OR
    b. Any bone marrow relapse after allogeneic SCT and must be ≥ 4 months from SCT at the time of CTL019 infusion with leukapheresis for CTL019 manufacturing performed at least 12 weeks after allogeneic SCT, OR
    c. Primary refractory as defined by not achieving a CR after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukemia OR
    d. Patients with Philadelphia chromosome positive (Ph+) ALL are eligible if they are intolerant to or have failed 2 lines of tyrosine kinase inhibitor (TKI) therapy, or if TKI therapy is contraindicated OR
    e. Ineligible for allogeneic SCT because of:
        - Comorbid disease
        - Other contraindications to allogeneic SCT conditioning regimen
        - Lack of suitable donor

- Prior SCT
- Declines allogeneic SCT as a therapeutic option after documented discussion about the role of SCT with a bone marrow transplantation physician who is not a member of the CTL019 study team.

2. For relapsed patients, CD19 tumor expression demonstrated in bone marrow or peripheral blood by flow cytometry within 3 months of study entry. For relapsed or refractory patients previously treated with blinatumomab, CD19 tumor expression must be demonstrated (via flow cytometry) at Screening.
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. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 times the upper limit of normal (ULN) for age.
   c. Total bilirubin < 2.0 mg/dL (with the exception of patients with Gilbert's syndrome. Patients with Gilbert's syndrome may be included if their total bilirubin is ≤ 4.0 mg/dL).
   d. Must have a minimum level of pulmonary reserve defined as ≤ grade 1 dyspnea and pulse oxygenation > 91% on room air.
   e. Left ventricular shortening fraction (LVSF) ≥ 28% confirmed by echocardiogram (ECHO), or left ventricular ejection fraction (LVEF) ≥ 45% confirmed by ECHO or multiple uptake gated acquisition (MUGA) within 7 days of Screening.
4. Life expectancy > 12 weeks.
5. Age < 26 years of age at the time of Screening.
6. Karnofsky (age ≥16 years) or Lansky (age < 16 years) performance status ≥ 50 at Screening.
7. Patients previously treated with blinatumomab who have detectable leukemia and documented CD19+ expression (via flow cytometry) and confirmed absence of CD19- leukemic blasts at Screening may be included. In this case, at least 1-week washout period must be applied from last dose of blinatumomab to start of leukapheresis. Patients previously treated with blinatumomab with no detectable MRD (i.e. MRD negative demonstrated by leukemic blasts < 0.01%) will be excluded.

   Note: blinatumomab must not be administered as a bridging therapy prior to CTL019 infusion while the patient is awaiting manufacture of CTL019.
8. Signed written ICF 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. Note: Please refer to Section 6.2.4 and Section 7.1.1.1 for prohibited concomitant medications and washout times to ensure adequate collection as well as the [Investigational Leukapheresis, Cryopreservation and Scheduling Manual] for specific collection procedures.
11. Patients with active CNS leukemia involvement defined as CNS-3 by CSF findings only are eligible but will have their CTL019 infusion delayed until CNS disease is reduced to CNS-1 or CNS-2 by CSF findings. Patients with other forms of active CNS-3 leukemic involvement such as CNS parenchymal or ocular disease, cranial nerve involvement or significant leptomeningeal disease are not eligible. However, such patients with other forms of CNS-3 leukemic involvement (non-CSF involvement) are eligible if there is documented evidence of disease stabilization for at least 3 months prior to CTL019 infusion. Patients must have no acute/ongoing neurologic toxicity > Grade 1 with the exception of a history of controlled seizures or fixed neurologic deficits that have been stable/improving over the past 3 months.

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 surface immunoglobulin (sIg) positive and kappa or lambda restricted positivity ALL, with French-American-British Classification System for Hematologic Disease 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. Prior treatment with any gene therapy product.
6. Prior treatment with any anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy, except for patients pre-treated with blinatumomab who fulfill inclusion criterion no. 8.
7. Presence of active replication of hepatitis B or hepatitis C (for detailed criteria see Appendix 2). Serology must be repeated if the interval between testing at Screening and CTL019 infusion exceeds 8 weeks.
8. HIV positivity as indicated by serology. Serology must be repeated if the interval between testing at Screening and CTL019 infusion exceeds 8 weeks.
9. Presence of grade 2 to 4 acute or extensive chronic GVHD.
10. Uncontrolled acute life threatening infection at Screening.

11. Previous or concurrent malignancy with the following exceptions:
    a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry).
    b. *In situ* carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study.
    c. A primary malignancy which has been completely resected and in CR for ≥ 5 years.
12. Intolerance to the excipients of the CTL019 cell product (i.e. dimethyl sulfoxide).
13. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History of myocardial infarction, angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment.
    - Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g. bifascicular block, Mobitz type II and third degree AV block).
    - LVEF < 45% as determined by ECHO or magnetic resonance angiography (MRA) or multiple uptake gated acquisition (MUGA).
    - New York Heart Association (NYHA) functional class III or IV (Chavey et al 2001).
14. Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.
15. Patient has an investigational medicinal product within the last 30 days prior to Screening.
16. 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 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, mycophenolate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-TNF, anti-IL-6 or anti-IL-6 receptor, systemic steroids).
    d. **Chemotherapy:**
        - TKIs 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.

17. Pregnant or nursing (lactating) women.

    NOTE: Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours before leukapheresis, lymphodepletion and prior to CTL019 infusion.

18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they agree to using highly effective methods of contraception from enrollment and for at least 12 months after the CTL019 infusion and until CAR T-cells are no longer present by qPCR on 2 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 tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 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.

19. Sexually active males must use a condom during intercourse from enrollment and for at least12 months after the CTL019 infusion and until CAR T-cells are no longer present by qPCR on 2 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

6.1.1 Investigational therapy

CTL019 is an autologous immunocellular therapy product that is comprised of CD3+ T cells that have undergone *ex vivo* T-cell activation, gene modification, expansion and formulation in infusible cryomedia. The transgene to be expressed via lentiviral vector transduction is a CAR targeted against the CD19 antigen. The CAR contains a murine scFv that targets CD19 linked to a transmembrane region derived from the CD8 receptor, which is linked to an intracellular bipartite signaling chain of TCR-ζ (or CD3-ζ) and 4-1BB intracellular signaling domains. The extracellular scFv with specificity for CD19 is derived from a mouse monoclonal antibody. T cells which are enriched from a patient leukapheresis unit are expanded *ex vivo* using commercially available magnetic beads that are coated with anti-CD3 and anti-CD28 monoclonal antibodies. The cells are transduced with the CD19 CAR lentiviral vector, which ensures that only peripheral WBCs 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 the release of the product for infusion.

Leukapheresis will be performed as outlined in Section 7.1.1.1 and in accordance with the Investigational [Leukapheresis, Cryopreservation and Scheduling Manual]. Manufacturing CTL019 cell product will start once the patient has been enrolled, undergone leukapheresis, and a leukapheresis product has been accepted by the Novartis designated manufacturing facility. The CTL019 cell product will be prepared and released by the manufacturing facility to the study site approximately 4-6 weeks after manufacturing has commenced, provided all required safety and quality release criteria have been met.

For details please refer to the [Investigational Product Handling Manual and Investigational Product Transport Manual] and the current version of the [Investigator's Brochure, current edition].

6.1.2 Pre-infusion evaluation

If any of the following criteria is met CTL019 infusion must be delayed until resolution to grade 1 (if applicable). If the period of delay is more than 4 weeks from completing lymphodepletion and there is no significant cytopenia (see Section 6.1.4) lymphodepletion should be repeated, and these criteria will need to be re-checked prior to CTL019 infusion:

1. Rapidly progressing primary disease (i.e. ALL).
2. Clinical evidence of CNS involvement by primary disease.
3. Laboratory abnormalities that, in the opinion of the investigator, may impact patient safety or the patient's ability to receive CTL019.
4. Following clinical abnormalities:
   - Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 90% or presence of progressive radiographic abnormalities on chest X-ray.
   - Cardiac arrhythmia not controlled with medical management.

   Hypotension requiring vasopressor support.
   - Active infection, as evidenced by positive blood cultures for bacteria, fungi, or PCR positivity for viral DNA in blood within 72 hours of CTL019 cell infusion, or clinical or radiographic evidence.
   - Active graft versus host disease (GVHD).
5. A significant change in clinical status that would, in the opinion of the investigator, increase the risk of AEs associated with CTL019.
6. Toxicities from chemotherapy (including lymphodepletion).
7. Concomitant medications and prohibited medications as described in Section 6.2.3 and Section 6.2.4.
8. Positive influenza test within 10 days prior to CTL019 infusion (please refer to Table 7-1). If the patient is positive for influenza, oseltamivir phosphate or zanamivir should administered for 10 days as preventative treatment (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their 10 day preventative treatment course prior to receiving CTL019. The test does not need to be repeated prior to CTL019 infusion however if flu-like or respiratory signs and symptoms are present, CTL019 infusion should be delayed until the patient is asymptomatic. For patients residing in the United States, Canada, Europe and Japan, influenza testing is required during the months of October through May (inclusive). For patients residing in the southern hemisphere such as Australia, influenza testing is required during the months of April through November (inclusive). For patients with significant international travel, both calendar intervals above may need to be considered.
9. Live vaccines must not be used in CTL019 recipients for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CTL019 treatment, and until immune recovery following treatment with CTL019.

6.1.3 Additional safety procedures prior to CTL019 infusion

Tumor lysis syndrome

The risk of tumor lysis syndrome (TLS) is dependent on disease burden. Patients will be closely monitored both before and after lymphodepleting chemotherapy and the CTL019 infusion, including blood tests for potassium and uric acid. Patients with elevated uric acid or high tumor burden will receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat).

Infections

Infection prophylaxis with regard to lymphodepletion and other additional treatments should follow local guideline. Infection prophylaxis is not recommended in the setting of CTL019 infusion. Please also refer to Section 6.2.1.2.

Cytokine release syndrome

The site must confirm that 4 doses of tocilizumab are on site and available for administration **prior to CTL019 infusion**. All other medications (except for tocilizumab or siltuximab administration), including steroids given to treat CRS, must be listed on the Concomitant Medication Case Report/Record Form (CRF). Tocilizumab or siltuximab should be reported on the "Dosage Administration Record - Tocilizumab" or "Dosage Administration Record - Siltuximab" electronic case report form (eCRF), respectively.

Premedication

Side effects from T cell infusions can include fever, chills and/or nausea. All patients should be pre-medicated with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine approximately 30 to 60 minutes prior to infusion. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved with acetaminophen (paracetamol). Steroids should NOT be used for premedication. It is recommended that patients NOT receive systemic corticosteroids other than physiologic replacement, except for serious emergency, since this may have an adverse effect on CTL019 expansion and function.

Supportive care

Local guidelines will be followed for the supportive care of immunosuppressed and chemotherapy treated patients. All blood products administered should be irradiated. For details about prohibited concomitant medications and non-drug therapies please refer to Section 6.2.4.

6.1.4 Additional study treatments

If patients have a white blood cell (WBC) count ≤ 1,000 cells/µL within 1 week prior to CTL019 infusion, lymphodepleting chemotherapy is **NOT** required.

Lymphodepletion should start 1 week before CTL019 infusion, which means that CTL019 will be infused 2 to 14 days after lymphodepletion depending on the lymphodepleting regimen. Lymphodepletion may be repeated in case CTL019 has been delayed by more than 4 weeks (see Section 6.1.2). The preferred regimen is as follows:

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

Side effects of fludarabine include severe neurological events of seizure, agitation, blindness, coma and death. Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune thrombocytopenia/idiopathic thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have been reported to occur after one or more cycles of treatment with fludarabine phosphate injection. Fludarabine may also severely decrease bone marrow function (Fludarabine full prescribing information).

Cyclophosphamide can cause cardiac dysfunction. Acute cardiac toxicity has been reported with doses as low as 2.4 g/m2 to as high as 26 g/m2, usually as a portion of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures. High doses of cyclophosphamide led in a few instances to severe, and sometimes fatal, congestive heart failure after the first dose. Severe marrow suppression is seen and occasional anaphylactic reactions have been reported. Hemorrhagic cystitis, pulmonary toxicity (pneumonitis, pulmonary fibrosis and pulmonary veno-occlusive disease leading to respiratory failure) and veno-occlusive liver disease may occur (Cyclophosphamide full prescribing information).

Alternative lymphodepletion regimen

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

No other regimen is allowed for lymphodepletion.

Female patients of childbearing potential must have a negative pregnancy test (urine or serum) within 24 hours prior to the start of lymphodepleting therapy. If the patient does not require lymphodepleting therapy, she should still have a negative pregnancy test at the required visit that takes place within 5 days prior to CTL019 infusion.

6.1.5 Treatment duration

Once CTL019 transduced viable T cells has been thawed and is at room temperature (20°C - 25°C), it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

For more details please refer to [Investigational Product Handling Manual] and the (Kymriah SmPC).

6.1.6 CTL019 dosing regimen

Based on the patient's weight reported at the time of leukapheresis/Screening (note: for patients with a historical leukapheresis product, the patient's weight reported at the time of Screening will be used), one of the 2 following allowable dose ranges will be prepared:

- For pediatric and young adult patients with r/r ALL whose weight is ≤ 50 kg, the targeted dose is 0.2 to 5.0 × 10^6 autologous CTL019 transduced viable T cells per kg body weight.

- For pediatric and young adult patients with r/r ALL whose weight is > 50 kg, the targeted dose is 0.1 to 2.5 × 10^8 autologous CTL019 transduced viable T cells.

Patients will be infused with the maximum cell dose within these ranges that can be individually manufactured. The CTL019 cell product will be released to the study site approximately 4-6 weeks after manufacturing has commenced, provided all required safety and quality release specifications have been met.

Products falling below the minimum values in the above allowable cell dose ranges will be evaluated for provision to the patient under exceptional circumstances after approval by Health Authorities for infusion.

Out of specification (OOS) product provision under exceptional circumstances

Given that CTL019 is an autologous advanced medicinal therapy, the final product may occasionally present with release testing result(s) that is/are OOS to the approved release testing. Where administration of such an OOS batch is requested by the treating physician based on a thorough benefit versus risk assessment, taking into account the alternative options for the patient and the consequences of not receiving CTL019 and administration of the product is considered necessary to avoid an immediate significant hazard to the patient, Novartis may provide the OOS batch upon agreement with the Health Authorities.

6.2 Additional treatment guidance

6.2.1 Recommended treatment of adverse events

Patients infused with CTL019 are at risk of developing a number of AEs that are related either to CTL019 itself, other therapies (e.g. immunochemotherapy) and conditions concurrent with the patient's primary disease. Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential toxicities. Physicians should consider hospitalization for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurological events. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Patients should be instructed to remain within proximity (i.e. within 2 hours' travel) of a qualified clinical facility for at least 4 weeks following infusion.

Following CTL019 infusion, patients can be discharged from the treating site only if, in the investigator's opinion, they do not demonstrate any AEs or worsening of underlying diseases.

This chapter describes the management of such AEs.

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

6.2.1.1 Cytokine release syndrome (CRS)

Data from CTL019 treated patients experiencing CRS show marked elevations in IL-6 and IFN-g. The symptoms generally occur 1-22 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 aspartate aminotransferase (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 Study CCTL019B2202 at clinical sites outside of Japan. If the patient experiences ongoing CRS despite administration of repeated anti-cytokine directed therapies with tocilizumab and siltuximab (if available in the country where the patient is being treated), steroids, and anti-T-cell therapies such as cyclophosphamide, anti-thymocyte globulin or alemtuzumab may be considered and need to be captured in the CRFs. 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 as presented in Table 6-1 and must be followed by Treating Physicians. TNF-α antagonists have been used with CTL019 associated CRS with little evidence for efficacy. Given the apparent lack of activity combined with their immunosuppressive effects, TNF antagonists are not recommended. This approach was designed to avoid life-threatening toxicities, while attempting to allow the CTL019 transduced cells to establish a proliferative phase which appears to correlate with tumor response. Patients will be required to remain proximal to the treating site for the first 21 days.

The management of CRS is based solely upon clinical parameters as described in Table 6-1. Ferritin, C-reactive protein and serum cytokine levels should NOT be used for clinical management decisions of CRS.

Cases of transient left ventricular dysfunction, as assessed by ECHO, have been reported in some patients with severe (grade 4) CRS. Therefore consideration should be given to monitoring cardiac function by ECHO during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

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 (prothrombin time, activated partial thromboplastin time (aPTT), and fibrinogen) should be more frequently monitored in this setting. CTL019 associated coagulopathy with or without clinical bleeding and hypofibrinogenemia is strongly recommended to be managed with cryoprecipitate of fibrinogen concentrate in addition to routine blood product support.

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 symptoms and severity	Management
Prodromal syndrome: • Low-grade fever, fatigue, anorexia.	• Observe in person, exclude infection. • Administer antibiotics per local guidelines if neutropenic. • Provide symptomatic support.
CRS requiring mild intervention - one or more of the following: • High fever • Hypoxia • Mild hypotension	• Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.

CRS requiring moderate to aggressive intervention - one or more of the following:
• Haemodynamic instability despite intravenous fluids and vasopressor support
• Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation
• Rapid clinical deterioration
	• Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed
	• Administer tocilizumab‡:
	  • Patient weight < 30 kg: 12 mg/kg IV over 1 hour
	  • Patient weight ≥ 30 kg: 8 mg/kg IV over 1 hour (max dose 800 mg)
	• Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement.
	• Limit to a maximum total of 4 tocilizumab doses

If no clinical improvement within 12 to 18 hours of the first tocilizumab dose	If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2 mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high-flow oxygen are no longer needed, then taper.
	If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures* for treatment of cytokine release syndrome. Limit to a maximum total of 4 tocilizumab doses.

CRS=cytokine release syndrome, IV=intravenous, NR=no response, TLS=tumor lysis syndrome

‡ Administer tocilizumab only via intravenous infusion (subcutaneous administration is not approved for CRS).

* Alternative measures: 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) only if available in the country the patient is located in, 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: Penn Grading Scale for Cytokine Release Syndrome

1	2	3	4
Mild reaction: Treated with supportive care such as anti-pyretics and anti-emetics.	**Moderate reaction:** Requiring intravenous therapies or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	**More severe reaction:** Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids* or low dose pressors, coagulopathy requiring fresh frozen plasma or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, continuous or bilateral positive airway pressure). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.	**Life-threatening complications** such as hypotension requiring high dose pressors (see Table 6-3 or hypoxia requiring mechanical ventilation.
• Marked elevations in IL-6, interferon gamma and less intensely TNF • Symptoms occur 1 to 22 days after cell infusion in ALL • Symptoms may include: High fevers, rigors, myalgia, arthralgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea, and hypoxia • The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (i.e. sepsis). The stop date of CRS is defined as the date when the patient has been afebrile for 24 hours and off vasopressors for 24 hours			

ALL=acute lymphoblastic leukemia, CRS=cytokine release syndrome, IL=interleukin, LFTs=liver function tests, TNF=tumor necrosis factor
*Defined as: multiple fluid boluses for blood pressure support

Table 6-3 Definition of high dose vasopressors

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

§ If institutional practice is to use flat dosing.

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

* Vasopressin and Septic Shock Trial (VASST) Norepinephrine equivalent equation:

NE dose (weight-based dosing) = [norepinephrine (mcg/kg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/kg/min)] + [phenylephrine (mcg/kg/min) ÷10] (online institutional guideline by MD Anderson Cancer Center 2018)

VASST Norepinephrine equivalent equation:

NE dose (flat dosing) = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10] (Russell et al 2008)

Source: Adapted from Lee et al 2014, Lee et al 2015, and Porter et al 2015

Note: pediatric weight adjustments should be taken into consideration.

6.2.1.2 Infections

Infection prophylaxis with regard to lymphodepletion and other additional treatments should follow local guidelines. As appropriate, prophylactic antibiotics should be administered and surveillance testing should be employed prior to and during treatment with CTL019.

Patients with active, uncontrolled infection should not start CTL019 treatment until the infection is resolved.

Patients should be monitored for signs and symptoms of infection and treated appropriately. As appropriate, prophylactic antibiotics should be administered and surveillance testing prior to and during treatment with CTL019 should be employed.

Institutional guidelines for vaccination (e.g. pneumococcus) should be followed before starting CTL019 therapy. As the lack of effective B cells after infusion makes the likelihood of a systemic infection considerable, vaccination with live virus vaccines should not be given for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CTL019 and until immune recovery following treatment with CTL019.

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

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

6.2.1.3 Neurological adverse events

Neurologic events, primarily reflective of encephalopathy and delirium, may occur after CTL019 infusion. These present clinically as signs and symptoms of varying severity including: confusion, disorientation, agitation, aphasia, somnolence and tremors. In severe cases seizures, motor weakness, incontinence, impaired consciousness, increased intracranial pressure, and cerebral edema may be concurrent to, following the resolution or in the absence of CRS. Patients should be monitored for neurologic events, diagnostically worked-up and managed depending on the underlying pathophysiology and in accordance to local standard of care.

Evaluation

- Thorough neurological examination, with frequent monitoring
- Diagnostic work up to evaluate potential secondary causes:

- Brain imaging (CT scan and/or MRI): to exclude intracranial hemorrhage, disease relapse, evidence suggestive of infection or cerebral edema.
- Lumbar puncture for cerebral spinal fluid (CSF) evaluation, if applicable.
- Chemistry laboratory testing
- Electroencephalography (EEG)

Management

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

6.2.1.4 Premedication and hypersensitivity including acute infusion reactions

Patients should be monitored for signs and symptoms of hypersensitivity following initiation of CTL019 infusion and treated appropriately. CTL019 is contraindicated in patients with known hypersensitivity to CTL019 or to any component of the product formulation.

As appropriate, prophylactic medications should be administered to minimize the risk of immediate hypersensitivity including acute infusion reactions. It is recommended to pre-medicate all patients with acetaminophen (paracetamol) and diphenhydramine or another H1 antihistamine within approximately 30-60 minutes prior to CTL019 infusion. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed for fever not responding to acetaminophen (paracetamol).

Steroids should not be used for premedication. It is recommended that patients NOT receive systemic corticosteroids other than physiologic replacement, except for serious emergency, since this may have an adverse effect on CTL019 expansion and function.

Patients should be monitored for signs and symptoms of hypersensitivity following initiation of CTL019 infusion and treated appropriately. CTL019 is contraindicated in patients with known hypersensitivity to CTL019 or to any component of the product formulation.

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

6.2.1.5 Tumor lysis syndrome (TLS)

The risk of TLS is dependent on disease burden. Patients should be closely monitored for signs and symptoms of TLS both before and after lymphodepleting chemotherapy and CTL019 infusion including relevant laboratory tests. To minimize risk of TLS, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior

to CTL019 infusion as indicated. Patients diagnosed with TLS should be managed according to local guidelines.

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

- Screening phase:
- Prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat), and increased oral/ 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 acute TLS (IV fluids and rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)
- Post-infusion monitoring phase:
- Frequent monitoring of the following laboratory tests (2 to 3 times/week for 3 weeks from start of lymphodepleting chemotherapy, then weekly): potassium, phosphorus, calcium, creatinine, and uric acid
- Encourage oral hydration

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

Laboratory TLS

Laboratory TLS is defined as two or more of the following values within 3 days before or in the days following CTL019 infusion:

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

Regimen:

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

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

Clinical TLS

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

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

6.2.1.6 Febrile neutropenia

Febrile neutropenia (significantly decreased neutrophil count with fever) may develop in the course of chemotherapy (including lymphodepletion) and may be concurrent with CRS. A febrile patient should be evaluated for infection (Section 2.6.1.2) and CRS (Section 2.6.1.1) and managed appropriately with fluids, antibiotics and supportive care, if applicable. In the event that the patient develops sepsis or systemic bacteremia following CTL019 cell infusion, appropriate cultures and medical management should be initiated. If a contaminated CTL019 product is suspected, the product can be retested for sterility using archived samples that are stored at the manufacturing site.

6.2.1.7 Prolonged depletion of normal B-cells and/ or hypogammaglobulinemia

Monitor immunoglobulin levels after treatment with CTL019, use infection precautions including antibiotic prophylaxis and immunoglobulin replacement as appropriate and per local standard of care.

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

6.2.1.8 Hematopoietic cytopenias lasting greater than or equal to 28 days

Hematopoietic cytopenias should be managed with standard measures of observation, blood product support growth factors and/or antibiotics as indicated and per local standard of care. Myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after CTL019 infusion or until CRS has resolved.

6.2.1.9 Generation of replication competent lentivirus (RCL)

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

Currently, it is not known how to manage a patient with confirmed RCL and therefore this should be addressed on a case by case basis. Some considerations are:

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

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

If uncontrolled T cell proliferation occurs (e.g., expansion of T cells in the absence of CD19 antigen), patients may be treated with corticosteroids such as methylprednisolone (2 mg/kg/d IV) 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 2.6.1.1.

6.2.1.11 Aggravation of graft versus host disease (GVHD)

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

6.2.1.12 Transmission of infectious agents

The risk associated with CTL019 is considered very low. Stringent precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of CTL019 are in place in compliance with principles of good manufacturing practices and regulatory guidelines. Details on shipping and storage conditions of CTL019 product and disposal are described in the US Prescribing Information (Kymriah US PI 2018).

6.2.1.13 Potential effects upon growth and development

The long-term effects of CTL019 therapy in pediatric patients are not known and therefore will be recorded. Such data will need to be interpreted in the context of the known effects of prior chemotherapy and radiation therapy in these pediatric patient populations.

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

Qualified center personnel must follow appropriate protocols for product handling to receive, thaw, and infuse the finished CTL019 product. Instructions are provided in the [Investigational Product Handling Manual].

6.2.2 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.

6.2.3 Concomitant medications

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

If the leukapheresis procedure was done more than 30 days prior to Screening then any concomitant medications taken as a result of related AE/SAE experienced by the patient within 24 hours of the procedure should be recorded.

At every visit following the screening visit up to the end of the study, concomitant medications will be recorded in the medical record and on the appropriate CRF. During selected trial phases, concomitant medication collection will be modified as outlined in Appendix 3: CTL019 Modified Data Reporting, CRF Completion Guidelines, and Table 6-4 below.

Modified collection of concomitant medication information during these periods is designed to capture CTL019-related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented.

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

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

Table 6-4 Concomitant medication reporting by trial phase

Trial phase	Inpatient/Intensive care unit (ICU)	Outpatient
Pre-treatment period (informed consent form (ICF) to lymphodepleting chemo/ pre-infusion)	Modified	Modified
Treatment period (lymphodepleting chemo/ pre-infusion through M12)	Modified	All concomitant medications

The following guidelines must be adhered to during the study:

- Granulocyte macrophage-colony stimulating factor should be avoided due to the potential to worsen CRS symptoms.
- Short acting granulocyte macrophage colony stimulating factor (GM-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 G-CSF are unknown. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after CTL019 infusion or until CRS has resolved.
- Steroids or other immunosuppressant drugs should NOT be used as pre-medication for CTL019 therapy (refer to Section 6.2.4) or following CTL019 infusion, except as required for physiological glucocorticoid replacement therapy, management of CRS, 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 6.2.1.1.

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

A significant number of CTL019 treated patients will require multiple days of inpatient and/or ICU care within 28 days after CTL019 infusion. These AEs are mostly due to CRS and MAS, although there may be also contribution from the preceding lymphodepleting chemotherapy (e.g., events such as febrile neutropenia or hematopoietic cytopenias). Cytokine release syndrome/MAS toxicity is an 'on-target' effect of the CTL019 cell expansion, activation and tumor cell killing.

A typical inpatient or ICU day can generate hundreds of data points and many therapeutic dose changes throughout a given day. These inpatient events and days are not scheduled protocol defined visits, although they are anticipated to occur in some patients. Revised inpatient data capture will be utilized for this study to systematically collect subsets of patient data to describe the management of safety events associated with CTL019 therapy for the purpose of:

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

This is done through a targeted collection of concomitant medications and laboratory data and CRS eCRF pages specifically designed to capture CTL019 related toxicity, severity, seriousness, causality, interventions and response/resolution following intervention. Details can be found in the CRF Completion Guidelines.

6.2.4 Prohibited medications and non-drug therapies

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

6.2.4.1 Medication restrictions prior to leukapheresis

For medication restrictions before leukapheresis, please refer to the recent [Investigational Leukapheresis, Cryopreservation and Scheduling Manual]. The medication restrictions provided in this document must be followed.

6.2.4.2 Medication restrictions prior to CTL019 infusion

1. **Steroids:** Therapeutic doses of steroids must be stopped > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: < 12 mg/m^2/day hydrocortisone or equivalent.
2. **Steroids or other immunosuppressant drugs** should NOT be used as pre-medication for CTL019 therapy (refer to Section 6.1.2, Pre-infusion Evaluation) 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 avoided just prior to and following CTL019 if possible or at least minimized.

3. **Allogeneic cellular therapy:** Any donor lymphocyte infusions must be completed > 6 weeks prior to CTL019 infusion
4. **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, mycophenolate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-TNF, anti-IL-6 or anti-IL-6 receptor, systemic steroids).
5. **Chemotherapy**:
   - TKIs 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.
6. CNS disease prophylaxis **or intrathecal therapy** must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)
7. Radiation therapy
   - 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.
8. **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
9. **Investigational therapies** must not be used at any time while on study until the first progression following CTL019 infusion
10. **Live vaccines** must not be used in CTL019 recipients for at least 6 weeks prior to lymphodepletion and during CTL019 treatment until immune recovery
11. **Granulocyte macrophage-colony stimulating factor (GM-CSF)** has the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after CTL019 infusion or until CRS has resolved. Short acting granulocyte colony stimulating factor (G-CSF) should not be given 72 hours prior to CTL019 infusion and long acting G-CSF should not be given 10 days prior to CTL019 infusion.

12. **Antiproliferative therapies,** other than lymphodepletion including low dose daily or weekly maintenance chemotherapy) should not be used within 2 weeks of leukapheresis and 2 weeks prior to infusion.

    Short acting drugs used to treat primary disease (e.g. hydroxyurea, tyrosine kinase inhibitors) must be stopped > 72 hours prior to leukapheresis and > 72 hours prior to CTL019.

6.2.5 Anticipated risks and safety concerns of the IMP

Appropriate eligibility criteria (Section 5.2 and Section 5.3) as well as criteria for stopping or pausing the study are included in this protocol (Section 4.5). Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs are also described (Section 6.2.1 and Section 7.1.1). Please refer to the [Investigator's Brochure, current edition] for preclinical toxicity and/or clinical data.

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

Patients with transaminase increase combined with TBIL increase may be indicative of potential drug-induced liver injury (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 × ULN combined with TBIL > 2.0 × ULN, or ALT or AST > 5.0 × ULN in isolation.
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 × baseline AND > 3.0 × ULN] OR [AST or ALT > 8.0 × ULN], whichever is lower, combined with [TBIL > 2 × baseline AND > 2.0 × ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as alkaline phosphatase (ALP) elevation > 2.0 × 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.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, TBIL, direct and indirect bilirubin, GGT, prothrombin time/international normalized ratio (INR) and ALP.
2. 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.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) such as a right upper quadrant ultrasound with duplex for flow, may be warranted.
4. 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).
5. Additional testing for other hepatotropic viral infection (cytomegalovirus, Epstein-Barr virus 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 8.1.2) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Upon ICF/assent completion, the patient will initiate Screening. Each patient is identified in the study by a 7 digit Patient Number (Patient No.), that is assigned sequentially at each site by the site Treating Physician 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 Patient No. consists of the 4 digit Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential 3 digit patient number suffixed to it such that each patient is numbered uniquely across the entire database. Upon signing the ICF, the patient is assigned to the next sequential Patient No. available to the Treating Physician through the Oracle remote data capture interface.

The Treating Physician 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 Patient No. must not be reused for any other patient and the Patient 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

The CTL019 cell product manufacturing will start once the patient has undergone leukapheresis (Section 7.1.1.1), leukapheresis product has been accepted by the Novartis manufacturing facility and patient deemed enrolled (after confirmation of eligibility criteria). The cell product will be prepared and released by the manufacturing facility to the site approximately 4-6 weeks after manufacturing has commenced provided that all required safety and quality release criteria of the final product have been met.

Upon release from the manufacturing facility, the cryopreserved CTL019 cell product is shipped to the Treating Physician. 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 Treating Physician must notify study Sponsor of any damaged or unusable CTL019 cell product that was supplied to the Treating Physician's site.

The CTL019 cell product will remain in storage until the patient 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 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 $\times 10^6$ autologous CTL019 transduced viable T cells per kg body weight (for patients $\leq$ 50 kg) and 0.1 to 2.5 $\times 10^8$ 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 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 label will have at least 2 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, 2 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 Study 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 Treating Physician 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 leukapheresis and the CTL019 product in line with the requirements outlined in 21 Code of Federal Regulations (CFR) 1271.250, 21 CFR 1271.290, 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 (GCP) 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 leukapheresis 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 Treating Physician 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.

The Treating Physician will dispose of used and unused CTL019 cell product, packaging, product labels per local institutional standard operating procedures, and return a copy of the completed drug accountability log to the study monitor. Please refer to [Investigational Product Handling Manual] for specific details on product destruction.

6.5.3.3 Handling of other study treatment

Not applicable.

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. 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. This information is submitted on an annual basis to the health authorities in annual reports. All CTL019 cell product disposition will be documented in the study files. Please refer to [Investigational Product Handling Manual] for details on product reconciliation.

7 Visit schedule and assessments

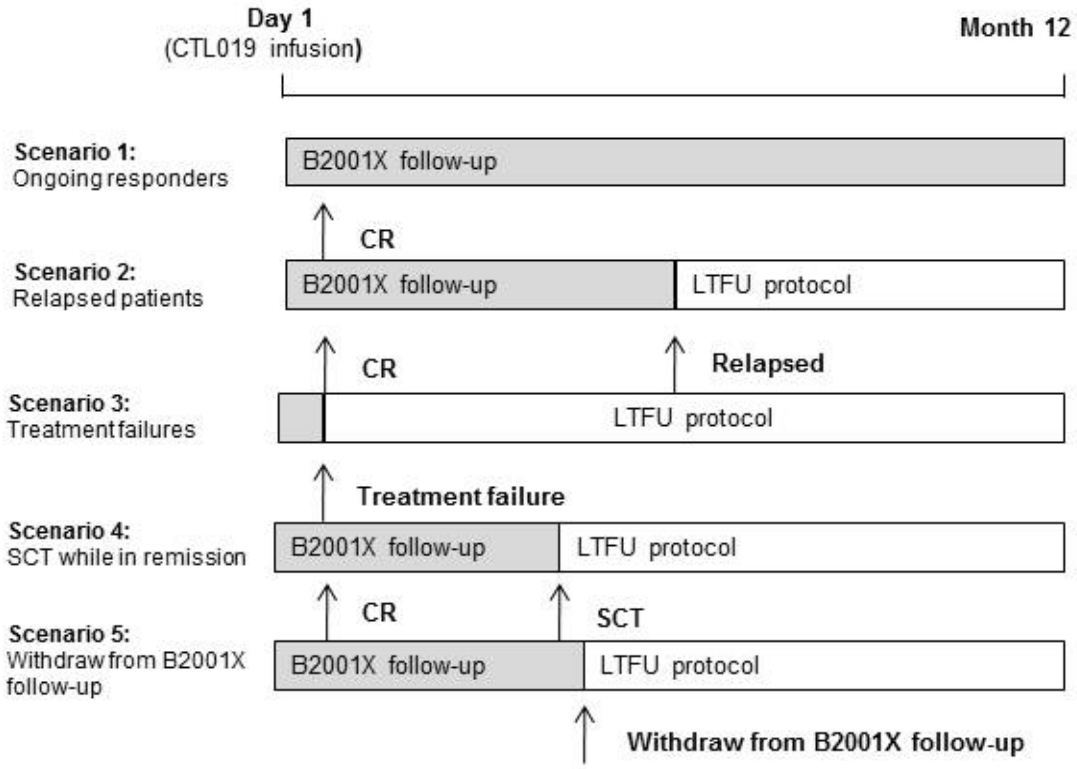
7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments from Screening through to the End of Treatment (EOT)/Early Withdrawal (Section 7.1.4). Required assessments are indicated with an "X" and the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. No CRF will be used as a source document.

For patients who discontinue early from the treatment, the patient will enter a LTFU study, under a separate protocol (CCTL019A2205B), to collect health authority requested data (e.g. delayed AEs etc.) as described in Section 7.1.5. The first visit in the LTFU protocol is determined according to the time since CTL019 infusion when the patient discontinued from treatment. Patients will continue to be followed until 15 years post-CTL019 infusion per health authority guidelines. It is anticipated that patients may leave this study and move to the LTFU protocol due to reasons including: treatment failure, relapse after remission, pursuing SCT while in remission, or withdrawal from the study.

The potential patient flow scenarios are presented in Figure 7-1.

Figure 7-1 Potential patient flow scenarios



Note: B2001X follow-up = CTL019B2001X study follow-up post infusion

CR=complete remission, LTFU= long-term follow-up, SCT=stem cell transplantation

Table 7-1 Visit evaluation schedule

Phase			Scr	Pre-treatment			Treatment and follow-up									End of treatment
Visit Name	**Category**	**Protocol reference section**	**Screening**	**Enrollment/Pre chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**								**End of treatment (Study CTL019B2001X)/ Start of LTFU study**
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**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 ±14d**	**M12 ±14d**
Obtain informed consent/assent	D	11.3	X													
IWRS/IRT	S	7.1.1.2	X	X			X		X	X		X	X	X M3 & M6 only	X	X
Patient history																
Demography	D	7.1.1	X													
Inclusion/exclusion criteria	D	5.2, 5.3	X													
Medical history	D	7.1.1	X													
Diagnosis and extent of cancer	D	7.1.1	X													
Cytogenetics/FISH/tumor immunophenotyping	D	7.1.1	X													
Prior antineoplastic therapy (Lines of therapy and number of prior allogenic SCT only should be recorded)	D	7.1.1	X													
Donor chimerism (prior allogeneic SCT patients only, or if unknown)	D	6.2.1.11, 7.1.1, 7.2.2.4	X													
Selected prior/concomitant medications	D	6.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	S	7.2.1.1	X			X		X		X		X	X	X	X	X

Phase	Category	Protocol reference section	Scr	Pre-treatment			Treatment and follow-up									End of treatment
Visit Name			Screening	Enrollment/Pre chemotherapy	Lymphodepleting Chemotherapy	Pre-infusion	Infusion	Post infusion								End of treatment (Study CTL019B2001X)/ Start of LTFU study
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	D28 ±4d	M2 M3 M4 M5 M6 ±14d	M9 ±14d	M12 ±14d
Performance status assessment	D	7.2.2.3	X			X		X		X		X	X	X	X	X
Height	D	7.2.2.2	X													
Weight	D	7.2.2.2	X			X										
Vital signs	D	7.2.2.1	X			X	X	X	X	X	X	X	X	X	X	X
Hospitalization (i.e. days of hospitalization)	D	7.2.4	Screening to Month 2													
Intervention																
Leukapheresis	D	7.1.1.1	X													
Lymphodepleting chemotherapy	D	7.1.2.2			X											
Other chemotherapy while on study	D	6.2.3	As clinically indicated													
CTL019 infusion prerequisite assessment	S	6.1.2, 6.1.3					X									
CTL019 T-cell infusion	D	6.1.6					X									
Antineoplastic therapies after CTL019 infusion or study discontinuation	D	6.2.3						X	X	X	X	X	X	X	X	X
Laboratory assessments																
Hematology	D	7.2.2.4	X		X		X		X	X		X	X	X	X	X
Chemistry ‡M2, M3 and M6 only	D	7.2.2.4	X		X		X		X	X		X	X	X‡		X

Phase			Scr	Pre-treatment			Treatment and follow-up									End of treatment
Visit Name	**Category**	**Protocol reference section**	**Screening**	**Enrollment/Pre chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**								**End of treatment (Study CTL019B2001X)/ Start of LTFU study**
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**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 ±14d**	**M12 ±14d**
Serum pregnancy test Must be performed on WOCBP using serum prior to leukapheresis, lymphodepletion, prior to CTL019 infusion and at the end of the trial.	D	7.2.2.4	X	X	X	X										X
Urine pregnancy test Between CTL019 infusion and end of the trial, WOCBP must be tested monthly using urine. At the Month 9 visit, tests kits will be provided to WOCBP to test at home for Month 10 and Month 11.	D	7.2.2.4					X						X	X	X	
HIV test	D	7.2.2.4	X													
Hepatitis B and C	D	7.2.2.4	X													
Influenza A and B	D	6.1.2, 7.1.2.3.1		Within 10 days of infusion												
Coagulation factors (PT, aPTT, INR, fibrinogen, D-dimer)	D	7.2.2.4	X		X		X			X		X	X			
Serum Ig levels (IgG, IgA, IgM)	D	7.2.2.4	X										X	X M3 & M6 only	X	X
MUGA/ECHO	D	7.1.1	X													
ECG	D	7.1.1	X				X									

Phase			**Scr**	**Pre-treatment**			**Treatment and follow-up**									**End of treatment**
Visit Name	**Category**	**Protocol reference section**	**Screening**	**Enrollment/Pre chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**								**End of treatment (Study CTL019B2001X)/ Start of LTFU study**
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**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 ±14d**	**M12 ±14d**
Urinalysis (see above for urine pregnancy tests)	D	7.2.2.4	X													
Pulse oximetry	D	7.2.2.1	X				X									
Disease assessments																
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 physical examination. For patients in CR/CRi, Month 3 and 6 recommended but not required		
MRD assessment in bone marrow aspirate by flow cytometry (includes normal B-cell counts and CD19 status) ‡ For patients previously treated with blinatumomab with no circulating blasts in peripheral blood, a CD19 assessment of the bone marrow will be performed prior to the initiation of lymphodepleting chemotherapy, as well as at the Screening Visit.	D	7.2.1	X	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 physical examination. For patients in CR/CRi, Month 3 and 6 recommended but not required		

Phase			**Scr**	**Pre-treatment**			**Treatment and follow-up**									**End of treatment**
Visit Name	**Category**	**Protocol reference section**	**Screening**	**Enrollment/Pre chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**								**End of treatment (Study CTL019B2001X)/ Start of LTFU study**
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**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 ±14d**	**M12 ±14d**
MRD assessment in bone marrow aspirate by q-PCR	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 physical examination. For patients in CR/CRi, Month 3 and 6 recommended but not required		
Tumor cell assessment by flow cytometry of peripheral blood (includes normal B-cell counts and CD19 status) ‡ For patients previously treated with blinatumomab, CD19 status must be checked (assessment of peripheral blood in the presence of circulating leukemic blasts or bone marrow in the absence of circulating leukemic blasts) prior to the initiation of lymphodepleting chemotherapy in addition to the check at the Screening visit.	D	7.2.1	X	X‡						X			X	X M3 & M6 only	X	X
Lymph node or other involved tissue aspirate or biopsy	D	7.2.1	As clinically indicated													

Phase			**Scr**	**Pre-treatment**			**Treatment and follow-up**									**End of treatment**
Visit Name	**Category**	**Protocol reference section**	**Screening**	**Enrollment/Pre chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**								**End of treatment (Study CTL019B2001X)/ Start of LTFU study**
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**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 ±14d**	**M12 ±14d**
CSF assessment/ 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 physical examination. Otherwise, as clinically indicated by the presence of neurological symptoms.
CNS Brain Imaging (MRI/CT)	S	7.2.1	As clinically indicated													
Extramedullary disease assessment (physical examination and CNS symptom assessment)	D	7.2.1.1, 7.2.1.2	X										X	X	X	X
Safety																
AEs	D	7.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancies and menstrual status Note: pregnancies includes collection of information of any pregnancies of partners of a male participant who received CTL019.	D	7.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RCL by VSV-g q-PCR (peripheral blood)	D	6.2.1.9, 7.2.2.4		X										X M3 & M6 only		X

Phase			Scr	Pre-treatment			Treatment and follow-up									End of treatment
Visit Name	**Category**	**Protocol reference section**	**Screening**	**Enrollment/Pre chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**								**End of treatment (Study CTL019B2001X)/ Start of LTFU study**
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**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 ±14d**	**M12 ±14d**
Immunogenicity																
Immunogenicity (serum)	D	7.2.2.4, 7.2.3, 10.4.2.3		X		X							X	X M3 & M6 only		X Note: If patient relapses before M12, then immunogenicity sample collection is required at relapse visit Note: Other unscheduled samples (e.g. related to safety events) may be taken as needed prior to M12
Immunogenicity (peripheral blood)	D	7.2.2.4, 7.2.3, 10.4.2.3		X		X							X	X M3 & M6 only		X Note: If patient relapses before M12, then immunogenicity sample collection required at relapse visit Note: Other unscheduled samples (e.g. related to safety events) may be taken as needed prior to M12

Phase			Scr	Pre-treatment			Treatment and follow-up									End of treatment
Visit Name	**Category**	**Protocol reference section**	**Screening**	**Enrollment/Pre chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**								**End of treatment (Study CTL019B2001X)/ Start of LTFU study**
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**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 ±14d**	**M12 ±14d**
Cellular kinetic assessments																
CTL019 cellular kinetics by q-PCR (peripheral blood)	D	7.2.2.4, 7.2.3, 10.5.12		X			X		X	X	X	X	X	X M3 & M6 only	X	X Note: If patient relapses before M12, then cellular kinetic sample collection is required at relapse visit Note: Other unscheduled samples (e.g. related to safety events or CRS) may be taken as needed prior to M12
CRS assessments by peripheral blood (CTL019 cellular kinetics)	D	7.2.3, 10.5.12					As clinically indicated dependent upon the presence and time-course of CRS and administration of anti-cytokine therapies. Sample collections for CTL019 cellular kinetic are mandated following CTL019 infusion at the time points indicated in Table 7-6. 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 clinically feasible as indicated in Table 7-9 and Table 7-10.									
End of phase disposition	D		X			X										X

Phase			**Scr**	**Pre-treatment**			**Treatment and follow-up**									**End of treatment**
Visit Name	**Category**	**Protocol reference section**	**Screening**	**Enrollment/Pre chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**								**End of treatment (Study CTL019B2001X)/ Start of LTFU study**
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**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 ±14d**	**M12 ±14d**

AE=adverse event, aPTT=activated partial thromboplastin time, CNS=central nervous system, CR=complete remission, CRi=complete remission with incomplete blood count recovery, CSF=cerebral spinal fluid, CT=computed tomography, ECG=electrocardiogram, ECHO=echocardiogram, FISH=Fluorescent *in situ* hybridization, HIV=human immunodeficiency virus, Ig=immunoglobulin, INR=international normalized ratio, IRT=interactive response technology, IWRS=interactive web response system, LTFU=long-term follow-up, MRD=minimal residual disease, MRI=magnetic resonance imaging, PT=prothrombin time, q-PCR=quantitative polymerase chain reaction, RCL=replication competent lentivirus, SCT=stem cell transplantation, VSV-g=vesicular stomatitis virus, glycoprotein, WOCBP=women of child-bearing potential

7.1.1 Screening phase

Anti-microbial prophylaxis treatment in these immunosuppressant r/r 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. It should be noted that blinatumomab must not be administered as a bridging therapy post leukapheresis and prior to CTL019 infusion while the patient is awaiting manufacture of CTL019.

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 ICF/assent form (Section 11.3) 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 (Section 6.2.3 and Section 6.2.4) and antineoplastic therapies (lines of therapy and number of prior allogenic SCT only should be recorded).
c. Physical examination (Section 7.2.1.1) including height, weight (Section 7.2.2.2), GVHD assessment (Section 6.2.1.11), vital signs (Section 7.2.2.1), extramedullary disease assessment and CNS symptom assessment (Section 7.2.1).
d. Performance status (Karnofsky [age ≥16 years] or Lansky [age < 16 years]) at the time of Screening (Section 7.2.2.3).
e. Standard ALL cytogenetics, fluorescent *in situ* hybridization (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) (Section 6.2.1.11 and Section 7.2.2.4).
g. Hematology panel (Section 7.2.2.4).
h. Chemistry panel (Section 7.2.2.4).
i. Coagulation panel (Section 7.2.2.4).
j. Urinalysis (Section 7.2.2.4).
k. Serum pregnancy test (if female of childbearing potential) within 24 hours prior to the leukapheresis procedure (Section 7.2.2.4).
l. Pregnancy and menstrual status (Section 7.2.2).
m. 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 (Section 7.2.2.4).

n. Hepatitis B and Hepatitis C test (test within 8 weeks of Screening; see Appendix 2 for interpretation of Hepatitis B results) (Section 7.2.2.4).
o. Serum Ig levels (IgG, IgA, IgM) (Section 7.2.2.4).
p. MUGA or ECHO (performed within 6 weeks of infusion) for LVSF/LVEF.
q. ECG.
r. Pulse oximetry (Section 7.2.2.1).
s. Bone marrow aspirate† (Section 7.2.1) for
   - Morphologic blast enumeration
   - Flow cytometry (B-cell numbers, tumor cell numbers, MRD assessment, CD19 assessment)
   - MRD assessment by q-PCR
t. Peripheral blood collection† for flow cytometry (B-cell and T-cell numbers, tumor cell numbers, and CD19 assessment) (Section 7.2.1).

   †Note: For patients previously treated with blinatumomab, a CD19 assessment (via flow cytometry) must be performed at the Screening Visit and the Pre-chemotherapy Visit. If no circulating blasts are identified in the peripheral blood, the CD19 expression (on leukemic blasts) assessment will subsequently be performed in the bone marrow. If circulating leukemic blasts are identified in the peripheral blood for assessment of CD19 expression, no bone marrow assessment is required.
u. Lumbar puncture (LP) for CSF cytology assessment (Section 7.2.1)
v. AEs (Section 8.1.1).
w. Hospitalization (i.e. days of hospitalization) (Section 7.2.4).
x. Other chemotherapy while on study if clinically indicated (Section 6.2.3).
y. Unscheduled assessments if clinically indicated (see below).
z. Contact the IRT (Section 7.1.1.2).
aa. End of phase disposition.

Unscheduled assessments

If clinically indicated at any study visit, the following unscheduled assessments may be performed:

- Lymph node or other involved tissue aspirate or biopsy (Section 7.2.1).
- CNS brain imaging (Section 7.2.1).

In addition, if clinically indicated at any study visit from Day 1 (day of infusion) onwards, the following unscheduled assessment may be performed:

- CRS assessments by peripheral blood (CTL019 cellular kinetics) from Day 1 (Section 7.2.3).

7.1.1.1 Leukapheresis assessment

Leukapheresis may only be collected at a Novartis qualified center.

Leukapheresis will be scheduled for cell procurement prior to final enrollment. It is strongly recommended that leukapheresis should be scheduled prior to any planned chemotherapy or non-physiologic dose of steroid administration as an absolute T-cell count (absolute lymphocyte count times the percentage of CD3 positive lymphocytes) ≤ 300/mm^3 will result in a poor T-cell collection and manufacturing failure.

The date of leukapheresis collection should be registered in IRT.

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 qualified leukapheresis center and the product is acceptable for manufacturing.

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

1. Peripheral blood absolute lymphocyte count (ALC) ≥ 500 µL (0.5×10^9/L), or if ALC < 500/ µL (< 0.5×10^9/L), then the absolute CD3 lymphocyte count must be ≥ 150/µL
2. No active or prior hepatitis B or C as indicated by serology within 30 days prior to leukapheresis collection (for detailed criteria see Appendix 2).
3. The following treatments/medications should be stopped as follows:
   - Cytotoxic chemotherapy drugs must not be given within 2 weeks of leukapheresis.
   - Intrathecal chemotherapy should be stopped ≥ 7 days prior to leukapheresis.
   - Steroids must be stopped > 72 hours or 5 half lives, whichever is greater prior to leukapheresis. However, physiological replacement doses of steroids (≤ 40 mg/day hydrocortisone or equivalent) are allowed.
   - Immunomodulatory drugs (e.g. interferons, TNF inhibitors): should be stopped ≥ 2 weeks prior to leukapheresis.

Per inclusion criterion no. 8 (Section 5.3), for patients previously treated with blinatumomab, a 1-week washout period must be applied from the last dose of blinatumomab to start of leukapheresis. It should be noted that blinatumomab must not be administered as a bridging therapy post leukapheresis and prior to CTL019 infusion while the patient is awaiting manufacture of CTL019.

Following informed consent and confirmation of all eligibility criteria, information on the patient's leukapheresis material, including sample sentinel vials collected from leukapheresis (when available), will be transferred to the Novartis designated manufacturing facility separately or together with the leukapheresis product. The manufacturing facility will then evaluate the patient's leukapheresis product for acceptance. Final enrollment is defined as the point at which the patient meets all clinical inclusion/exclusion criteria, and the patient's leukapheresis product is accepted for manufacturing. Please refer to the Leukapheresis Key Requirements within the most recent [Investigational Leukapheresis, Cryopreservation and 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. Drugs prohibited prior to leukapheresis and CTL019 infusion are described in Section 8.1.1 and Section 6.2.4.

For patients developing grade 2 to 4 acute GVHD or extensive 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.

7.1.1.2 Eligibility screening and enrollment

For detailed enrollment procedures, including use of IRT, please refer to the [IRT User Manual]. The enrollment period for the study will continue until enrollment completion of approximately 80 patients or up to the Sponsor's (i.e. Novartis) decision to end the trial.

Only following informed consent and confirmation of all eligibility criteria will information on the patient's leukapheresis product be transferred to the Novartis designated manufacturing facility.

Leukapheresis can only be performed after patient consent has been obtained as described in Section 7.1.1.1. At the time when manufacturing of CTL019 is required, a Novartis designated manufacturing facility will then evaluate the patient's leukapheresis product for acceptance and notify the infusion site. The acceptance of the product will be registered in IRT by Novartis personnel.

Enrollment is defined as the point at which a patient meets all clinical inclusion/exclusion criteria and the patient's leukapheresis product is received and accepted by the manufacturing facility. The patient is then enrolled using the same Patient No. assigned at Screening by the site Treating Physician or designated staff. Once assigned, the Patient No. must not be reused for any other patient and the Patient 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 ICF/assent form is obtained and again after eligibility is confirmed.

The IRT will subsequently be contacted on Day 1, 4, 7, 14, 28, Month 3, 6, 9 and 12 as outlined in Table 7-1.

Guidance for patients undergoing repeat manufacturing

If a patient was enrolled but manufacturing failed, there will be the possibility of a second attempt to manufacture CTL019 cells.

Assessments completed after original enrollment to confirm the patient is still clinically eligible for the second manufacturing: Enter data into unscheduled CRF pages, e.g. vital signs, Karnofsky and Lansky performance status, cardiac imaging, local ECG, hematology, blood chemistry, pregnancy test, local HIV, viral serology, coagulation, serum immunoglobulin, urinalysis, microscopic analysis, CSF lumbar assessment for suspicion of CNS involvement, flow cytometry, biomarker assessment. Please refer to the CRF filing guidelines for additional information.

7.1.1.3 Information to be collected on screening failures

The reason for not being enrolled will be entered in the clinical database. The demographic information, ICF/assent form, leukapheresis collection information, Inclusion/Exclusion pages, any AEs leading to patient discontinuation, and any AEs that meet reporting criteria in Appendix 3 (i.e. 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

The assessments to be performed in the pre-treatment phase are detailed in the sub-sections below as well as in Table 7-1.

7.1.2.1 Enrollment/Pre-chemotherapy evaluation visit (Week minus 16 to Day minus 1)

Before the scheduled lymphodepleting chemotherapy regimen is to begin, the patient will undergo blood collection for safety assessments and other assessments as listed below at the enrollment/pre-chemotherapy evaluation visit. Blood draws can be collected at any time after ICF is signed up until before the lymphodepleting chemotherapy is scheduled. Viably frozen samples from the leukapheresis material as well as the CTL019 product will be collected at the manufacturing site for correlative studies.

At the enrollment/pre-chemotherapy visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2).
- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4).
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4).
- Influenza A or B (within 10 days prior to infusion as described in Section 7.1.2.3.1).
- For patients previously treated with blinatumomab, a CD19 assessment (via flow cytometry) must be performed at the Pre-chemotherapy Visit in addition to the assessment at the Screening Visit (Section 7.2.1). If no circulating blasts are identified for the CD19 expression assessment of the peripheral blood, the assessment will subsequently be performed in the bone marrow. If circulating blasts are identified in the peripheral blood for the assessment of CD19 expression, no bone marrow assessment is required.
- AEs (Section 8.1.1).
- Serum pregnancy test (if female of childbearing potential) (Section 7.2.2.4).
- Pregnancy and menstrual status (Section 7.2.2).
- RCL by VSV-g q-PCR (peripheral blood) (Section 6.2.1.9 and Section 7.2.2.4).
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3).
- Immunogenicity (serum and peripheral blood) (Section 7.2.3).
- Other chemotherapy while on study (if clinically indicated) (Section 6.2.3).
- Unscheduled assessments if clinically indicated (Section 7.1.1 and Section 7.2.1).

7.1.2.2 Lymphodepleting chemotherapy visit (Day minus 14 to Day minus 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 also be eligible. The use of additional chemotherapy prior to the recommended pre-infusion chemotherapy will be at the discretion of the Treating Physician and dependent on the patient's disease burden.

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 IV daily for 4 doses) and cyclophosphamide (500 mg/m^2 IV 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 1 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.

At the lymphodepleting chemotherapy evaluation visit, patients will undergo the following assessments:

- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Serum pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancy and menstrual status (Section 7.2.2)
- Lymphodepleting chemotherapy (as described above)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- Coagulation factors (prothrombin time, aPTT, INR, fibrinogen, D-dimer) (Section 7.2.2.4)
- Influenza A or B (within 10 days prior to infusion as described in Section 7.1.2.3.1)
- AEs (Section 8.1.1)
- Unscheduled assessments if clinically indicated (Section 7.1.1 and Section 7.2.1)

7.1.2.3 Pre-infusion visit (Day minus 1 plus 1 day)

On the day prior to or day of the scheduled CTL019 infusion, patients will undergo the following assessments:

- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Physical examination (Section 7.2.1.1)

- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Weight (Section 7.2.2.2)
- Vital signs (Section 7.2.2.1)
- Serum pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancy and menstrual status (Section 7.2.2)
- Influenza A or B (within 10 days prior to infusion as described below in Section 7.1.2.3.1)
- AEs (Section 8.1.1)
- Disposition at end of pre-infusion visit
- Immunogenicity (peripheral blood and serum) (Section 7.2.3)
- Unscheduled assessments if clinically indicated (Section 7.1.1 and Section 7.2.1)

7.1.2.3.1 Influenza diagnostic test

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 Europe, Canada 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 follow-up phase

7.1.3.1 Infusion visit (Day 1)

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.

Infusion visit assessments are listed at the end of this section. Blood tests and final CTL019 infusion pre-requisites (including an ECG and a rapid influenza test) will be checked prior to infusion. Vital signs will be monitored prior to and following the infusion.

CTL019 transduced T cells will be given as a single dose of 0.2 to 5.0×10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5×10^8 CTL019 transduced viable T cells (for patients > 50 kg). Details on the administration of the CTL019 infusion are found in Section 6.1.

At the infusion visit (Day 1), patients will undergo the following assessments as also outlined in Table 7-1:

- Contact the IRT (Section 7.1.1.2)
- Urine pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancy and menstrual status (Section 7.2.2)
- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Vital signs (prior to and following CTL019 infusion per Section 7.2.2.1)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- CTL019 infusion pre-requisite assessment (Section 6.1.2)
- CTL019 infusion (see Section 6.1.6 for administration details)
  - CTL019 transduced T cells will be given as a single dose of 0.2 to 5.0 × 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 × 10^8 CTL019 transduced viable T cells (for patients > 50 kg)
- Hematology (prior to infusion per Section 7.2.2.4)
- Chemistry (prior to infusion per Section 7.2.2.4)
- Coagulation factors (prothrombin time, aPTT, INR, fibrinogen, D-dimer) (prior to infusion per Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- ECG (Section 7.2.2.5)
- Pulse oximetry (Section 7.2.2.1)
- AEs (Section 8.1.1)
- Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.2 Post-infusion visits: Day 2, Day 4 (plus or minus 1 day), Day 7 (plus or minus 1 day), Day 11 (plus or minus 1 day), Day 14 (plus or minus 3 days)

The assessments to be performed at each visit in the first 14 days following CTL019 infusion are described by visit in the sub-sections below as well as in Table 7-1.

7.1.3.2.1 Day 2 visit assessments

At the Day 2 visit, patients will undergo the following assessments:

- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)

- AEs (Section 8.1.1)
- Pregnancy and menstrual status (Section 7.2.2)
- Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.2.2 Day 4 (plus or minus 1 day) visit assessments

At the Day 4 visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2)
- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Vital signs (Section 7.2.2.1)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- AEs (Section 8.1.1)
- Pregnancy and menstrual status (Section 7.2.2)
- Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.2.3 Day 7 (plus or minus 1 day) visit assessments

At the Day 7 visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2)
- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- Coagulation factors (prothrombin time, aPTT, INR, fibrinogen, D-dimer) (Section 7.2.2.4)
- Tumor cell assessment by flow cytometry of peripheral blood (including normal B-cell counts and CD19 status) (Section 7.2.1)
- AEs (Section 8.1.1)

- Pregnancy and menstrual status (Section 7.2.2)
- Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.2.4 Day 11 (plus or minus 1 day) visit assessments

At the Day 11 visit, patients will undergo the following assessments:

- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Vital signs (Section 7.2.2.1)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- AEs (Section 8.1.1)
- Pregnancy and menstrual status (Section 7.2.2).
- Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.2.5 Day 14 (plus or minus 3 days) visit assessments

At the Day 14 visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2)
- Prior/concomitant medications (Section 6.2.3 and Section 6.2 4)
- Physical examination (Section 7.2.1.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- Coagulation factors (prothrombin time, aPTT, INR, fibrinogen, D-dimer) (Section 7.2.2.4)
- AEs (Section 8.1.1)
- Pregnancy and menstrual status (Section 7.2.2)
- Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.3 Post-infusion visit (Day 28 plus or minus 4 days)

At the Day 28 visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2)

- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)

Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)

- Vital signs (Section 7.2.2.1)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- Immunogenicity (serum and peripheral blood) (Section 7.2.3)
- Coagulation factors (prothrombin time, aPTT, INR, fibrinogen, D-dimer) (Section 7.2.2.4)
- Serum Ig levels (IgG, IgA, IgM) (Section 7.2.2.4)
- Aspirate morphology (Section 7.2.1)
- MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
- MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
- Tumor cell assessment by flow cytometry of peripheral blood (including normal B-cell counts and CD19 status) (Section 7.2.1)
- CSF assessment/LP (Section 7.2.1)
- Extramedullary disease assessment (physical examination and CNS symptom assessment) (Section 7.2.1.1 and Section 7.2.1.2)
- AEs (Section 8.1.1)
- Urine pregnancy test (if female of childbearing potential) (Section 7.2.2.4).
- Pregnancy and menstrual status (Section 7.2.2)
- Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.4 Post-infusion visits (Month 2 plus or minus 14 days; Month 3 plus or minus 14 days; Month 4 plus or minus 14 days; Month 5 plus or minus 14 days; Month 6 plus or minus 14 days)

The assessments to be performed at each post-infusion visit from Month 2 to Month 6 are described by visit in the sub-sections below as well as in Table 7-1.

Following initial achievement of CR or CRi, peripheral blood and extramedullary disease assessments (physical examination 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 Day 28 visit assessment, a bone marrow aspirate and CSF assessment/LP 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 examination and CNS symptom assessments).

If patients were in CR or CRI at the Day 28 visit assessment, it is recommended (but not mandatory) that an aspirate, LP/CSF assessment and lymph node aspirate or biopsy (if accessible) is performed at Month 3 and Month 6 for tumor response assessments.

If patients relapse at any time prior to Month 12, then cellular kinetics and immunogenicity sample collection is required at the relapse visit (Section 7.1.4.1).

7.1.3.4.1 Month 2 (plus or minus 14 days) visit

At the Month 2 visit, patients will undergo the following assessments:

- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Hospitalization (i.e. days of hospitalization) (Section 7.2.4)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- Extramedullary disease assessment (physical examination and CNS symptom assessment) (Section 7.2.1)
- AEs (Section 8.1.1)
- Urine pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancies and menstrual status (Section 7.2.2)
- CSF assessment/LP (Section 7.2.1)
    - If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination
    - Otherwise as clinically indicated by presence of neurological symptoms.
- If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination, the following assessments are also required:
    - Aspirate morphology (Section 7.2.1)
    - MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
    - MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
    - Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.4.2 Month 3 (plus or minus 14 days) visit

At the Month 3 visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2)
- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- Immunogenicity (serum and peripheral blood) (Section 7.2.3)
- Serum Ig levels (IgG, IgA, IgM) (Section 7.2.2.4)
- Extramedullary disease assessment (physical examination and CNS symptom assessment) (Section 7.2.1)
- AEs (Section 8.1.1)
- Urine pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancies and menstrual status (Section 7.2.2)
- RCL by VSV-g q-PCR (peripheral blood) (Section 6.2.1.9 and Section 7.2.2.4)
- Tumor cell assessment by flow cytometry of peripheral blood (including normal B-cell counts and CD19 status) (Section 7.2.1)
- CSF assessment/LP (Section 7.2.1)
    - If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination
    - Otherwise as clinically indicated by presence of neurological symptoms.
- If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination, the following assessments are also required:
    - Aspirate morphology (Section 7.2.1)
    - MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
    - MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
- If patients were in CR or CRi at the Day 28 visit, the following assessments are recommended but not mandatory:
    - Aspirate morphology (Section 7.2.1)

- MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
- MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
- Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.4.3 Month 4 (plus or minus 14 days) visit

At the Month 4 visit, patients will undergo the following assessments:

- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Extramedullary disease assessment (physical examination and CNS symptom assessment) (Section 7.2.1)
- AEs (Section 8.1.1)
- Urine pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancies and menstrual status (Section 7.2.2)
- CSF assessment/LP (Section 7.2.1)
  - If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination
  - Otherwise as clinically indicated by presence of neurological symptoms.
- If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination, the following assessments are also required:
  - Aspirate morphology (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
  - Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.4.4 Month 5 visit

At the Month 5 visit, patients will undergo the following assessments:

- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)

- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Extramedullary disease assessment (physical examination and CNS symptom assessment) (Section 7.2.1)
- AEs (Section 8.1.1)
- Urine pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancies and menstrual status (Section 7.2.2)
- CSF assessment/LP (Section 7.2.1)
  - If patients were not in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination
  - Otherwise as clinically indicated by presence of neurological symptoms
- If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination, the following assessments are required:
  - Aspirate morphology (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
  - Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.4.5 Month 6 (plus or minus 14 days) visit

At the Month 6 visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2)
- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- Immunogenicity (serum and peripheral blood) (Section 7.2.3)

- Serum Ig levels (IgG, IgA, IgM) (Section 7.2.2.4)
- Extramedullary disease assessment (physical examination and CNS symptom assessment) (Section 7.2.1)
- AEs (Section 8.1.1)
- Urine pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancies and menstrual status (Section 7.2.2)
- RCL by VSV-g q-PCR (peripheral blood) (Section 6.2.1.9 and Section 7.2.2.4)
- Tumor cell assessment by flow cytometry of peripheral blood (including normal B-cell counts and CD19 status) (Section 7.2.1)
- CSF assessment/LP (Section 7.2.1)
  - If patients were not in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination
  - Otherwise as clinically indicated by presence of neurological symptoms.
- If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination, the following assessments are required:
  - Aspirate morphology (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
- If patients were in CR or CRi at the Day 28 visit, the following assessments are recommended but not mandatory:
  - Aspirate morphology (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
  - Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.3.5 Post-infusion visit (Month 9 plus or minus 14 days)

At the Month 9 visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2)
- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)
- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)

- Hematology (Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- Serum Ig levels (IgG, IgA, IgM) (Section 7.2.2.4)
- Extramedullary disease assessment (physical examination and CNS symptom assessment) (Section 7.2.1)
- AEs (Section 8.1.1)
- Urine pregnancy test (if female of childbearing potential), and provision of urine pregnancy test kits to cover Month 10 and Month 11 (Section 7.2.2.4).
- Pregnancies and menstrual status (Section 7.2.2)
- Tumor cell assessment by flow cytometry of peripheral blood (including normal B-cell counts and CD19 status) (Section 7.2.1)
- CSF assessment/LP (Section 7.2.1)
  - If patients were not in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination
  - Otherwise as clinically indicated by presence of neurological symptoms.
- If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination, the following assessments are required:
  - Aspirate morphology (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
  - Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.4 End of treatment visit including study completion and premature withdrawal

The EOT visit for each patient will be 12 months from the date of their infusion if they complete all scheduled visits. If a patient discontinues early from the study, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the EOT visit will be performed. An EOT Disposition CRF page should be completed, giving the date and reason for stopping the study.

At the Month 12 (±14d) EOT/Early Withdrawal Visit, patients will undergo the following assessments:

- Contact the IRT (Section 7.1.1.2)
- Prior/concomitant medications (Section 6.2.3 and Section 6.2.4)
- Physical examination (Section 7.2.1)
- Performance status (Karnofsky (age ≥16 years) or Lansky (age < 16 years) (Section 7.2.2.3)
- Vital signs (Section 7.2.2.1)

- Antineoplastic therapies administered after the CTL019 infusion or following study discontinuation (Section 6.2.3)
- Hematology (Section 7.2.2.4)
- Chemistry (Section 7.2.2.4)
- CTL019 cellular kinetics by q-PCR (peripheral blood) (Section 7.2.3)
- Immunogenicity (serum and peripheral blood) (Section 7.2.3)
- Serum Ig levels (IgG, IgA, IgM) (Section 7.2.2.4)
- Extramedullary disease assessment (physical examination and CNS symptom assessment) (Section 7.2.1)
- AEs (Section 8.1.1)
- Serum pregnancy test (if female of childbearing potential) (Section 7.2.2.4)
- Pregnancies and menstrual status (Section 7.2.2)
- RCL by VSV-g q-PCR (peripheral blood) (Section 6.2.1.9 and Section 7.2.2.4)
- Tumor cell assessment by flow cytometry of peripheral blood (including normal B-cell counts and CD19 status) (Section 7.2.1)
- CSF assessment/LP (Section 7.2.1)
  - If patients were not in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination
  - Otherwise as clinically indicated by presence of neurological symptoms.
- If patients were **not** in CR or CRi at the Day 28 visit assessment and this is the first visit where clinical evidence of remission is observed by blood and physical examination, the following assessments are required:
  - Aspirate morphology (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by flow cytometry (includes normal B and T-cell counts and CD19 status) (Section 7.2.1)
  - MRD assessment in bone marrow aspirate by q-PCR (Section 7.2.1)
  - Unscheduled assessments if clinically indicated (Section 7.1.1, Section 7.2.1, Section 7.2.3)

7.1.4.1 Relapse evaluation

If at any time 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 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

b. Immunogenicity (humoral and cellular)
c. CTL019 cell characterization on peripheral blood (cellular kinetics by q-PCR)
d. 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 follow-up visit schedule until the institution of systemic antineoplastic therapy.

7.1.4.2 Criteria for premature patient withdrawal from the study

Patients must be followed according to the visit schedule (Table 7-1) to ensure adequate data are collected for the proper assessment of study primary and secondary objectives. Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the Treating Physician at any time.

For patients who are lost to follow-up, the Treating Physician 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 lost to follow-up should be recorded as such on the CRF.

It is anticipated that patients may leave the study due to reasons including:

- Treatment failure.
- Relapse after remission.
- Pursuing hematopoietic stem cell transplant while in remission.
- Patient voluntary withdrawal from the primary follow-up.

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 Long-term follow-up

As a single administration study, patients are followed on this study for **1 year** post-infusion for safety and efficacy evaluations. A LTFU study for the follow-up of lentiviral vector safety and efficacy will continue under a separate protocol. Patients will continue to be followed until 15 years post-CTL019 infusion per health authority guidelines.

Under the LTFU 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 LTFU

protocol at the time of study completion/discontinuation (separate ICFs/assent forms will be provided for this protocol). One to 2 times a year patients will visit the clinical site for a physical examination and medical history (including concomitant medications and AEs) with careful attention to features possibly related to lentiviral associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurological disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, or new incidence of other hematologic disorders. In addition, laboratory samples will be drawn to evaluate routine safety endpoints, CTL019 vector persistence and RCL. Efficacy assessments of the status of patients' primary malignancy will also be performed to evaluate the proportion of patients who relapse, experience disease progression or die.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments will be performed according to the Novartis guidelines for efficacy evaluation in ALL studies (Appendix 1), which is based on the NCCN guidelines (NCCN 2017, v1), Cheson et al 2003 and Appelbaum et al 2007. The local Treating Physician assessments will be used for sensitivity analysis for select efficacy endpoints.

Table 7-2 Imaging or disease assessment collection plan – treatment phase

Procedure	Screening / Pre-infusion	Post-infusion Assessments
Bone marrow aspirate 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 examination 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 (EOT)
Lymph node or other involved tissue aspirate or biopsy	As clinically indicated	As clinically indicated
CSF assessment/ LP 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 examination 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 examination and CNS symptoms) Recommended (but not required) at Month 3 and 6 and as clinically indicated

Procedure	Screening / Pre-infusion	Post-infusion Assessments
CNS brain imaging (CT/MRI)	As clinically indicated	As clinically indicated
Extramedullary disease assessment (physical examination and CNS symptom assessment)	Mandated	Mandated: Months 1, 2, 3, 4, 5, 6, 9, 12 (EOT)
Flow cytometry of peripheral blood (B-cell, T-cell, tumor cell, CD19 assessment)	Mandated	Mandated: Day 7 and Months 1, 3, 6, 9, 12 (EOT)
Abbreviations: CNS=central nervous system; CR=complete remission; CRi=complete remission with incomplete blood count recovery; CSF=cerebral spinal fluid; CT=computed tomography; EOT=end of treatment, LP=lumbar puncture; MRD=minimal residual disease; MRI=magnetic resonance imaging; physical examination=physical examination		

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 is required. In addition, the physical examination will 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 examinations will be performed. Physical examinations will be performed at the time-points indicated in Table 7-1.

Significant findings that were present prior to the signing of ICF/assent form 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 AE page of the patient's CRF. For visits where disease response is assessed (Month 1, 2, 3, 4, 5, 6, 9, 12), assessment results will be recorded on the physical examination 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), assessment results will be recorded on the CNS disease response CRF page.

7.2.2 Safety assessments

Safety will be monitored by assessing physical examination, laboratory abnormalities as well as collecting AEs at every visit. For details on AE collection and reporting, refer to Section 8.1.1.

Female patient reproductive status (menstrual status and pregnancy information) will be updated at all study visits (see Table 7-1).

7.2.2.1 Vital signs

The following vital signs will be assessed at the time-points indicated in Table 7-1: temperature, blood pressure, pulse measurements, and respiratory rate. Pulse oxygen will additionally be assessed at the Screening Visit and the Infusion Visit (Day 1).

7.2.2.2 Height and weight

Height will be measured in centimeters (cm) at the Screening Visit only. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing) will be measured at the Screening Visit and at the pre-infusion visit (Day -1) using a consistent method.

7.2.2.3 Performance status

The performance status of patients will be assessed using the Karnofsky/Lansky performance scales (Table 7-3) at the time-points indicated in Table 7-1.

Table 7-3 Karnofsky/Lansky Performance Scales

Karnofsky Scale (age ≥ 16 years)		**Lansky Scale (age < 16 years)**	
Able to carry on normal activity and to work; no special care needed.		Able to carry on normal activity; no special care is needed	
100	Normal no complaints; no evidence of disease	**100**	Fully active
90	Able to carry on normal activity; minor signs or symptoms of disease	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort; some signs or symptoms of disease	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.		Mild to moderate restriction	
70	Cares for self; unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance, but is able to care for most of his personal needs	**60**	Ambulatory up to 50% of the time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
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 Laboratory evaluations

Screening and other laboratory assessments will be performed accordingly to Table 7-4 and Table 7-5.

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 7.1.1. For all laboratory assessments that occur on Day 1, these should be performed prior to CTL019 infusion unless indicated otherwise.

The Treating Physician 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 Treating Physician 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 7-4 Local clinical laboratory parameters collection plan

Test category	Test name
Hematology	Hematocrit, hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelets, red blood cells (RBCs), white blood cells (WBCs) 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 or urea, creatinine, sodium, potassium, calcium, total protein, albumin, total bilirubin (TBIL), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), magnesium, phosphorus, lactate dehydrogenase, ferritin, C-reactive protein and uric acid.
Urinalysis	Macroscopic panel (dipstick) (bilirubin, blood, glucose, ketones, leukocytes esterase, nitrite, potential of hydrogen, protein, specific gravity) If macroscopic panel is abnormal then perform microscopic panel (RBCs, WBCs, casts, crystals, bacteria, epithelial cells)
Coagulation	Prothrombin time or International normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer
Pregnancy screen	Serum or urine tests
Viral serology	Rapid influenza A and B, hepatitis C RNA qualitative test or antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, human immunodeficiency virus (HIV; if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines)
Cerebral spinal fluid (CSF)	WBCs, presence or absence of lymphoblasts, RBCs, glucose, protein
Additional assessments	Serum immunoglobulin (Ig) 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

Table 7-5 Central clinical laboratory parameters collection plan

Test category	Test name
CTL019 assessments (includes T cells)	CTL019 cellular kinetics by q-PCR (peripheral blood)
RCL (VSV-g)	VSV-g q-PCR (peripheral blood)
Immunogenicity	Prevalence and incidence of immunogenicity against CTL019 (peripheral blood and serum)
q-PCR=quantitative polymerase chain reaction, RCL=replication competent lentivirus, VSV-g=vesicular stomatitis virus, glycoprotein	

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

7.2.2.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as described in Table 7-1, i.e. at Screening and Day 1 (Infusion Visit). Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or AEs as appropriate.

7.2.2.6 Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing performed. Additional pregnancy testing might be performed if requested by local requirements.

For the frequency of pregnancy testing and type of sample (serum or urine) please refer to Table 7-1.

For pregnancy reporting requirements and follow-up of the newborn refer to Section 8.1.6.

For more information about the effects of CTL019 on reproduction please refer to the recent [Investigator's Brochure, current edition].

7.2.3 Cellular kinetics

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

Table 7-6 CTL019 cellular kinetics by q-PCR in peripheral blood collection log

Day/scheduled time point*	CTL019 cellular kinetic sample no.	Sample volume
W−16 to D−1 enrollment/pre-chemotherapy	101	3 mL
D1, 10 min ± 5 min post-infusion	102	3 mL
D4 ± 1 day	103	3 mL
D7 ± 1 day	104	3 mL
D11 ± 1 day	105	3 mL
D14 ± 3 days	106	3 mL
D28 ± 4 days	107	3 mL
M3 ± 14 days	108	3 mL
M6 ± 14 days	109	3 mL
M9 ± 14 days	110	3 mL
M12 ± 14 days	111	3 mL
Unscheduled (cellular kinetic samples related to CRS)[a]	1001	3 mL/collection
Unscheduled (cellular kinetic samples at relapse)[b]	2001	3 mL
Unscheduled (cellular kinetic samples related to safety events)***	3001	3 mL/collection

Day/scheduled time point*	CTL019 cellular kinetic sample no.	Sample volume

CRS=cytokine release syndrome, DNA=deoxyribonucleic acid, q-PCR=quantitative polymerase chain reaction, RCL=replication competent lentivirus, VSV-g=vesicular stomatitis virus, glycoprotein

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

[a] Unscheduled cellular kinetic samples related to a CRS event whereby anti-cytokine therapy is not administered are uniquely, sequentially numbered 1001, 1002, etc. See Table 7-9 and Table 7-10 for anti-cytokine CRS related cellular kinetic collections.

[b] Unscheduled cellular kinetic samples related to relapse should be collected along with a corresponding immunogenicity sample and are uniquely numbered 2001
(refer to Table 7-7 and Table 7-8).

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

Note: RCL by VSV-g q-PCR is performed at the relevant time points (see Table 7-1) using DNA extracted from these samples.

Table 7-7 Immunogenicity serum sample collection log

Day/scheduled time point*	Sample volume
W−16 to D−1 enrollment/pre-chemotherapy	5 mL
D−1 + 1 day	5 mL
D28 ± 4 days	5 mL
M3 ± 14 days	5 mL
M6 ± 14 days	5 mL
M12 ± 14days	5 mL
Unscheduled (at relapse)**	5 mL
Unscheduled (e.g. related to safety events)	5 mL/collection

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

**In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding cellular kinetic sample (refer to Table 7-6)

Table 7-8 Immunogenicity peripheral blood sample collection log

Day/scheduled time point*	Sample volume**
W−16 to D−1 enrollment/pre-chemotherapy	10 mL
D−1 + 1 day	10 mL
D 28 ± 4 days	10 mL
M3 ± 14 days	10 mL
M6 ± 14 days	10 mL
M12 ± 14 days	10 mL
Unscheduled (at relapse)***	10 mL
Unscheduled (e.g. related to safety events)	10 mL/collection

Day/scheduled time point*	Sample volume**

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

** All patients' sample volumes will be adjusted for size with patient conditions.

***In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding cellular kinetic sample (refer to Table 7-6)

Sample collections for CTL019 cellular kinetics are mandated following CTL019 infusion at the time-points indicated in Table 7-6. 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, as indicated in Table 7-9 and Table 7-10.

Table 7-9 CTL019 cellular kinetics in patients treated with tocilizumab during CRS

Day/scheduled time point*/**	CTL019 cellular kinetic sample no.	Sample volume (whole blood)
D1 1 hour ± 15 min post infusion	201	2 mL
D2 ± 2 hours	202	2 mL
D3 ± 4 hours	203	2 mL
D7 ± 1day	204	2 mL
D1 (pre-dose; second infusion)	205	2 mL
D2 ± 2 hours from second infusion	206	2 mL
D3 ± 4 hours	207	2 mL
D7 ± 1day	208	2 mL
D1 (5 to 15 minutes pre-dose; additional infusion)	209	2 mL
D2 ± 2 hours	210	2 mL
D3 ± 4 hours	211	2 mL
D7 ± 1day	212	2 mL
Additional ***	213, 214, 215, 216	2 mL

*All measurement times are relative to tocilizumab infusion unless otherwise specified.

**Samples may be collected as needed dependent upon administration of tocilizumab, if clinically feasible.

*** Additional cellular kinetic samples collected in the event more than 2 tocilizumab doses are administered should follow additional cellular kinetic collection and numbering schedule.

Table 7-10 CTL019 cellular kinetics in patients treated with siltuximab during CRS

Day/scheduled time point*/**	CTL019 cellular kinetic sample no.	Sample volume (whole blood)
D1 1 hour ± 15 min post infusion	501	2 mL
D2 ± 2 hours	502	2 mL
D3 ± 4 hours	503	2 mL
D7 ± 1day	504	2 mL
D1 (pre-dose; additional infusion)	505	2 mL
D2 ± 2 hours from additional infusion	506	2 mL
D3 ± 4 hours	507	2 mL
D7 ± 1day	508	2 mL
Additional ***	509, 510, 511, 512	2 mL

*All measurement times are relative to siltuximab infusion unless otherwise specified.

**Samples may be collected as needed dependent upon administration of siltuximab, if clinically feasible.

*** Additional cellular kinetic samples collected in the event more than 1 siltuximab dose is administered should follow additional cellular kinetic collection and numbering schedule.

7.2.3.1 Analytical method

The assays to be utilized for various cellular kinetic assessments include q-PCR assay to detect CTL019 transgene (transgene copies/microgram DNA) in peripheral blood. Details regarding collection and processing of the samples used in these assays will be provided in the Central Laboratory Manual.

7.2.4 Hospitalization

Hospitalization data, i.e. number of days in hospital, should be captured from the day of Screening up to Month 2 for the patient as indicated 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 ICF.
- Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- 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 8.1.2 are not required.

8 Safety monitoring and reporting

8.1 Definition of adverse events and reporting requirements

8.1.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the infusion of CTL019.

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

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

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

Adverse events (including laboratory 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 AE.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.1.2):

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, with the exception of CRS, which will follow Table 6-1. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, life-threatening and fatal, corresponding to Grades 1 - 5, will be used.
2. Its relationship to the study treatment and other investigational treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 8.1.2 for definition of SAE) and which seriousness criteria have been met.

5. Action taken regarding with study treatment. All AEs must be treated appropriately. Treatment may include treatment interruption or withdrawal.
6. Its outcome, i.e., its recovery status or whether it was fatal.

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

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

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

Adverse event reporting should be continued as specified in Table 14-4.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of underlying malignancy with fatal outcome should be reported as a SAE irrespective of causality, if it occurs within 30 days post CTL019 infusion. After 30 days, progression of underlying malignancy should be reported as a 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. For SAE reporting see also Section 8.1.2. For definition of progression of disease, refer to the Lugano Guideline (Cheson et al 2015).

Adverse events separate from the progression of malignancy (e.g., deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as **per usual guidelines used for** such events with proper attribution regarding relatedness to the treatment.

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease. Detailed AE reporting requirements during the screening, pre-treatment, treatment, follow-up periods are outlined in Table 14-4.

8.1.2 Serious adverse events

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

- Fatal
- Life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect

Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines). All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

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

8.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent must be reported to Novartis safety within 24 hours of learning of its occurrence for the duration as specified in in Table 14-4. Additional SAE reporting

requirements, including those for the periods of screening, pre-treatment, follow-up and post-treatment, are also outlined in Table 14-4. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Cases of fatal disease progression will continue to not be entered as SAE, but entered as Death into the clinical trial database.

- The following AEs must be treated as SAEs and reported within 24 hours:
  - Grade ≥ 4 neurotoxicity
  - Any death irrespective of causality within 30 days after CTL019 infusion
  - Death after 30 days if at least possibly related to CTL019

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

If the SAE is not previously documented in the [Investigator's Brochure, current edition] or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

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

8.1.4 Adverse events of special reporting requirements

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

8.1.5 Duration of adverse event reporting

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

8.1.6 Pregnancy reporting

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 on a Clinical Trial Pregnancy Form and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the

possible relationship to CTL019 infusion any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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

8.1.7 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

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

8.2 Additional safety monitoring

8.2.1 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 / AEs 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 6 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 14-6 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 14-7. Repeat liver chemistry tests (ALT, AST, total bilirubin (TBL), prothrombin time/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (Section 4.6), 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, CT or MRI, as appropriate) and pathology assessments, gastroenterologist's or hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease, obtaining a history of exposure to environmental chemical agents.

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

8.2.2 Renal safety monitoring

The following 2 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 ≥ 1g/g or ≥100 mg/mmol, OR new onset dipstick proteinuria ≥ 3+ OR new onset dipstick hematuria ≥ 3+ (after excluding menstruation, urinary tract infection, extreme exercise, or trauma)

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

Every renal laboratory trigger or renal event as defined in Table 14-8 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 14-9 (Appendix 7).

8.2.3 Follow up of secondary malignancy

For patients treated with CTL019, treating physician/ healthcare providers should contact Novartis if the patient develops a secondary malignancy. Upon clinical confirmation secondary malignancy, blood samples should be collected for cellular kinetic analysis by qPCR and flow cytometry. Two tubes of blood are requested: 10 ml sample of peripheral blood mononuclear cells (PBMCs) in a sodium heparin collection tube and 6 ml of blood in an EDTA tube. Novartis

strongly recommends collection of biopsy samples from secondary malignancies for exploratory analysis. Additional details for sample handling and shipping are outlined in the laboratory manual.

8.3 Warnings and precautions

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

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
- 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 Treating Physician, 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 a Treating Physician's meeting, Novartis personnel (or designated Contract Research Organization) will review the protocol and CRFs with the Treating Physicians 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 GCP, 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 Treating Physician 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 Treating Physician must also keep the original signed ICF/assent form (a copy is given to the patient).

The Treating Physician 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 Treating Physician staff will enter the data required by the protocol into the eCRFs.

The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Treating Physician site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the Treating Physician staff.

The Principal Treating Physician 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 Contract Research Organization) 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 Treating Physician site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history and AEs will be coded using the MedDRA terminology.

For EDC studies, after final database lock, the Treating Physician 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.

The primary and selected secondary analyses will be performed after all patients have received CTL019 infusion and completed 6 months post-infusion of CTL019. All other data will be assessed when patients enrolled in the study complete the 1 year follow-up period after infusion, or prematurely discontinue before the end of the follow-up period. 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 definition of the analysis sets are not dependent on the age of the patient. All tables, figures and listings will be presented by 1 treatment arm of CTL019.

10.1.1 Screened Set

The Screened Set comprises all patients who have signed ICF/assent form 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 patient's leukapheresis product is received and accepted by the manufacturing facility.

10.1.3 Full Analysis Set

The Full Analysis Set (FAS) comprises all enrolled patients who have received infusion of CTL019.

10.1.4 Safety Set

The Safety Set (SAF) comprises all patients who received infusion of CTL019. By this definition the FAS and the SAF will be the same for this study.

10.1.5 Cellular Kinetic Analysis Set

The pharmacokinetic/cellular kinetic analysis set (PAS) consists of patients in the FAS who have at least 1 sample providing evaluable cellular kinetic data. The PAS will be used for summaries (tables and figures) and listings of cellular kinetic data.

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

10.1.6 Per-Protocol Set

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

Major protocol deviations leading to exclusion from the PPS include:

- No diagnosis of ALL at baseline;
- Prior therapy does not match with study protocol 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 2.0×10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) or 1.0×10^8 autologous CTL019 transduced viable T cells (for patients > 50 kg) will also be excluded.

The detailed exclusion criteria of PPS will be determined prior to final clinical database lock.

Screening disposition information will be summarized based on Screened set. The Enrolled Set will be used to summarize pre-treatment disposition data and to list whether patients received CTL019 or not. The primary objective will be evaluated using the SAF. All other safety analysis will be performed on the SAF. The FAS will be used as the efficacy analysis set.

10.2 Patient demographics/other baseline characteristics

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

Patients failing prior anti-neoplastic medications/therapies will be summarized.

Patients will be classified by the following baseline characteristics and summarized using absolute and relative frequencies.

a. their body weight stratum (i.e., ≤ 50 kg and > 50 kg)
b. the prior allogeneic SCT status (i.e., with prior SCT, without prior SCT), and
c. their prior response status into:
    - Primary refractory: If patient never had a morphologic CR prior to the study
    - Relapsed disease: If patient had a CR from other therapy and relapsed prior to the study

All SAEs reported after signing the ICF until the day of infusion, according to the guidelines provided in Section 8.1.1 will be considered a part of medical history and listed for the FAS.

The lymphodepleting chemotherapy is considered as a study treatment although not the investigational treatment and any AE occurring after start of the chemotherapy until the day of CTL019 infusion will be reported by severity for the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The total cells count (in 10^8 cells/kg), total CTL019 transduced viable T cells count (in 10^8 cells/kg), actual percentage volume (%) infused and dose interruptions will be listed and summarized using descriptive statistics. Patients will be categorized as below, within or above the prescribed dose range by body weight stratum (i.e. $\leq$ 50 kg and > 50 kg).

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 term and preferred term (PT). Transfusion during the study will be listed. In addition, whether patients have received anti-cytokine medications for the management of CRS will be summarized.

10.4 Primary objective

The primary objective of the study is to evaluate descriptively the safety of CTL019 therapy. The assessment of safety will include all treatment-emergent AEs including SAEs, and laboratory abnormalities occurring from Screening through to EOT (Month 12)/Early Withdrawal. Treatment-emergent AEs are defined as AEs that started or worsened after the infusion of CTL019. The primary analysis will be based on the SAF.

10.4.1 Variable

The primary variable is overall treatment-emergent AEs (including SAEs, and laboratory abnormalities).

10.4.2 Analysis of primary variable

10.4.2.1 Adverse events

For all AE summaries, the SAF will be used. All listings and tables will be presented by 1 treatment arm of CTL019. Reporting of AEs will be based on MedDRA and CTCAE version 4.03 or higher.

All treatment-emergent AEs will be recorded and listed. The incidence of overall treatment-emergent AEs (new or worsening from baseline visit of infusion) will be summarized as follows: overall by system organ class (SOC) and PT, overall by SOC, PT and severity (based on CTCAE grades), suspected treatment-related AEs by SOC and PT, SAEs by SOC and PT. Deaths will be listed by reason. Furthermore, the number and percentage of patients with the most frequent AEs (percentage cut-off to be determined in the statistical analysis plan (SAP)) will be summarized.

A patient with multiple CTCAE grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of CTCAE grade 3 and 4 AEs will be summarized separately.

10.4.2.2 Laboratory abnormalities

For laboratory tests covered by the CTCAE, the study 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, as appropriate, may be specified in the SAP.

10.4.2.3 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 titer fold-change from baseline will be determined for each patient. The assay for humoral immunogenicity will be a cell-based assay, detecting antibodies that bind to a Jurkat cell line transfected with the CTL019 construct. This cell line stably expresses the complete CTL019 sequence and can be used to detect antibodies that bind to any epitope on the extracellular domain of the protein. [redacted]

10.4.3 Statistical hypothesis, model, and method of analysis

No statistical hypothesis testing will be done for the primary variables.

10.4.4 Handling of missing values/censoring/discontinuations

All available data will be used in these evaluations of safety. No imputation will be done for missing AE data. In case a high number of premature discontinuations occur in this study a sensitivity analysis of some endpoints e.g. key AEs will be performed using the Kaplan-Meier (KM) method. This method will be used in order to provide adjusted incidence rates over the study period, censoring patients that discontinue prematurely.

10.4.5 Supportive analyses

No supportive analyses are planned for the primary objective.

10.4.5.1 Subgroup analysis

The summaries of overall AEs (regardless of relationship to study treatment) will by repeated on the SAF for 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, Relapsed disease
- Prior SCT therapy: 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, as appropriate.

10.5 Secondary objectives

The secondary 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 LTFU protocol, if appropriate.

10.5.1 Proportion of patients who achieve complete remission during 6 months after CTL019 infusion

The objective is based on the CR (CR or CR with incomplete blood count recovery, i.e. CR or CRi) rate as determined by Sponsor assessment during the 6 months after CTL019 administration. The CR 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 Month 6. Best overall disease response will be assigned according to the following order:

- CR
- CRi
- NR
- Unknown

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 > 1.0×10^9/L, and Platelets > 100×10^9/L, and Circulating blasts < 1% **Extramedullary disease** No evidence of extramedullary disease (by physical examination and central nervous system (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 ≤ 1.0×10^9/L, and/or Platelets ≤ 100×10^9/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 examination, and CSF assessment by LP, is required at the first time a CR or CRi is demonstrated. Bone marrow biopsy/aspirate and in 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 examination 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 Month 3 and Month 6).

CRs in patients with ALL have been observed to take place within 1 month after infusion with CTL019. The onset of CRs 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 examination and CNS symptom assessment) and circulating blasts in peripheral blood are < 1%. In order for the best remission rate 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 examination 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 proportion of patients who achieve a CR, which includes CR or CRi during the 6 months after CTL019 infusion, among all patients in the FAS, will be summarized along with 2-sided exact 95% CI. In addition, the proportion among patients who achieved CR or CRi will also be summarized in the similar manner.

10.5.2 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% CIs. In addition, the percentage of patients who achieved CR or CRi will also be summarized. The time of proceeding to SCT is defined as the time of commencing the conditioning regimen as required for hematopoietic SCT. This definition applies to all analyses.

10.5.3 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% CIs. In addition, the percentage will also be summarized for all patients who achieved CR or CRi.

All patients who proceed to SCT post CTL019 infusion before Month 6 will be listed.

10.5.4 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, whichever occurs first.

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 (with or without lymphodepleting chemotherapy) (also see below for handling SCT)
- Event after at least 2 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 (Committee for Medicinal Products for Human Use (CHMP) 2010). If a patient received SCT after a CR or CRi, relapse 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 after SCT will be used for the calculation of DOR as a sensitivity analysis.

An 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).

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 (CIs) using the cumulative incidence function or the KM method.

For Method 1 and Method 3, the cumulative incidence function is used to estimate the probability of the event of interest in the presence of the competing risks (Kim et al 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% CIs 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.

[redacted] Baseline disease characteristics and post-baseline factors (e.g. time to CR/CRi, MRD) 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% CI will be provided. [redacted]

All analyses will be based on the FAS.

10.5.5 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 other than reinfusion with one or more additional CTL019 dose/s (with or without lymphodepleting chemotherapy) (also see below for handling SCT)
- Event after at least 2 missing scheduled disease assessments

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, in the FAS. The distribution function of RFS will be estimated using the KM method. The median RFS along with 95% CIs will be presented if appropriate.

10.5.6 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
- Relapse
- Treatment failure: Defined as NR in the study and discontinuation from the study due to any of the following reasons:
  - AE (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 cut-off, 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 the FAS. The distribution function of EFS will be estimated using the KM method. The median EFS along with 95% CIs will be presented if appropriate.

10.5.7 Overall survival (OS)

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

In case a patient is alive, OS 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

The OS will be assessed in all patients from the FAS. The distribution function of OS will be estimated using the KM method. The median OS along with 95% CIs will be presented if appropriate.

10.5.8 Response at Day 28 (plus or minus 4 days)

Proportion of patients attaining CR or CRi at Day 28 ± 4 days post CTL019 infusion, among all patients in the FAS, will be summarized along with exact 95 % CI.

10.5.9 Impact of baseline tumor burden on response

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

10.5.10 Quality of response using MRD assessments

The quality of response using MRD 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 q-PCR) will be summarized descriptively.

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

10.5.11 Other safety objectives

For all safety analyses, the SAF will be used. All listings and tables will be presented by 1 treatment arm of CTL019.

10.5.11.1Laboratory assessments

All laboratory assessments will be summarized by pre- and post- infusion periods and visits as well as listed by patient for the SAF.

All laboratory abnormalities occurring post-infusion comprises of the category of treatment emergent AEs and are reported as a part of the primary analysis as specified in Section 10.4.2.2. Any laboratory abnormality occurring pre-infusion will only be flagged in the respective listing.

10.5.11.2B-cell level

The levels of B 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 CR will exhibit B-cell aplasia. Timing of B-cell recovery will be summarized.

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

10.5.11.3 Other safety data

Other safety data comprises vital signs, ECGs, pulse oximetry, ECHO will be reported descriptively and listed using the SAF, as appropriate.

10.5.11.4 CTL019 product characteristics

Selected clinical outcomes will be summarized descriptively by CTL019 product characteristics (e.g. T-cell subsets, transduction efficiency, etc.).

10.5.12 Cellular kinetics

CTL019 concentrations in the peripheral blood, as measured by q-PCR, will be listed, graphed, and summarized by time point.

The cellular kinetic parameters listed in Table 10-3 along with other relevant cellular kinetic parameters will be estimated from the individual concentration versus time profiles using a non-compartmental approach within the modeling study Phoenix® (Pharsight, Mountain View, CA). The non-quantifiable concentrations will be imputed to zero for concentration summaries, and will not be included for estimation of cellular kinetic parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and parameter derivations.

Table 10-3 Non-compartmental cellular kinetic parameters

Parameter	Definition
AUC 0 - T_{max}	The AUC from time zero to T_{max} in peripheral blood (copies/µg x days)
AUC T_{max} - 28d and M3	The AUC from time T_{max} to Day 28 and Month 3 or other disease assessment days, in peripheral blood (copies/µg x days)
AUC 0 - 28d and M3	The AUC from time zero to Day 28 and Month 3 or other disease assessment days, in peripheral blood (copies/µg x days)
C_{max}	The maximum (peak) observed in peripheral blood drug concentration after single dose administration (copies/µg)
C_{last}	The last observed quantifiable concentration in peripheral blood (copies/µg)
T_{max}	The time to reach maximum (peak) peripheral blood drug concentration after single dose administration (days)
$T_{1/2}$	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
T_{last}	The time of last observed quantifiable concentration in peripheral blood (days)

Descriptive statistics of the cellular kinetic parameters will be summarized by mean, standard deviation, coefficient of variation, geometric mean, CV% geometric mean, median, 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 of maximum concentration (C_{max}) and area under the curve $(AUC)_{0\text{-}28d}$ of CTL019 in the blood with CRS grade will be assessed.

The relationship between anti-cytokine treatment, use of steroids, occurrence of immunogenicity or other relevant covariates and cellular kinetics will be explored.

Populated based approaches could be implemented to evaluate the cellular kinetic and response (PD) data. Further details will be specified in the SAP.

10.6 Interim analysis

No interim analysis is planned for the program.

10.7 Sample size calculation

There is no formal sample size calculation performed for this study. This study aims to provide pediatric/young adult patients with r/r B-cell ALL the opportunity to be treated with CTL019 after closure of enrollment to the Novartis single-arm Phase II clinical trial CTL019B2202. The primary objective is to evaluate descriptively the safety of CTL019 and no testing of hypothesis will be performed.

The sample size is projected based on the availability of eligible patients who have provided acceptable leukapheresis product of non-mobilized cells to the manufacturing site and by the capacity of manufacturing CTL019 product in the Novartis facility at an average of 2 slots per month. It is anticipated that the recruitment duration will be ~2 years. Based on this assumption, and assuming that the average number of slots may increase as the study progresses, it is anticipated that approximately 80 patients will be enrolled in this study.

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 GCP, with applicable local regulations (including European Directive 2001/20/EC and US CFR Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the treating physician and IRB/IEC/REB

The study and the proposed ICF must be reviewed and approved by a properly constituted IRBs/IECs/REBs before study start. Prior to study start, the Treating Physician is required to sign a study 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 study and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical QA 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 ICF or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the 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 ICF 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 Treating Physicians, in a separate document, a 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 Treating Physician 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.

Sexually active males will be asked to provide an Information for Female Partner form to their partner.

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 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 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 study, 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 Treating Physician (s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of QA 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 study necessary for the reconstruction and evaluation of the study. 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 study.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Principal Treating Physician. The study CRF is the primary data collection instrument for the study. The Treating Physician should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The Treating Physician should retain records of the changes and corrections to paper CRFs. The Treating Physician/institution should maintain the study 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 Treating Physician/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 study unless Treating Physician provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The Treating Physician 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 ICF/assent form 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 Study adherence

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

12.1 Amendments to the study

Any change or addition to the study can only be made in a written study 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 study amendments, the Treating Physician 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 study. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

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14 Appendices

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

Document history

Not applicable.

List of abbreviations

ALL	Acute lymphoblastic leukemia
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
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 remission
EFS	Event-free survival
FDA	United States Food and Drug Administration
LP	Lumbar puncture
MNC	Mononuclear cells
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NR	No response
OS	Overall survival
PCR	Polymerase Chain Reaction
RBC	Red blood cell
RFS	Relapse-free survival
SCT	Stem cell transplantation
WBC	White blood cell

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 2017 v1) and further supported by the workshop report on acute leukemia from American Society of Hematology (Appelbaum et al 2007) and the International Working Group guideline for acute myeloid leukemia (Cheson et al 2003).

The Cheson International Working Group guideline and Appelbaum American Society of Hematology 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 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 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
  - Central nervous system (CNS) disease
  - Other extramedullary sites
- 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.

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 (NR) 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 white blood cell (WBC) $< 0.5 \times 10^9$/L preventing an accurate assessment of differential count), but the bone marrow result is showing complete remission (CR) status (per Table 14-1 definition). 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 electronic case report form ((e)CRF).

Extramedullary disease is to be assessed via physical examination, cerebral spinal fluid (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.

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, LP should be performed as clinically indicated by the presence of neurological 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/µL in CSF with presence of lymphoblasts.
- CNS-3 is defined as WBC of 5/µL or greater with presence of lymphoblasts.

If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC $\geq$ 5/µL in CSF with blasts, then compare the CSF WBC/red blood cell (RBC) ratio to the blood WBC/RBC ratio. If the CSF 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 (computed tomography scan or magnetic resonance imaging 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 (ALL) (NCCN 2017 v1, Cheson et al 2003).

The classification of mediastinal response in NCCN 2017 v1 based on radiographic assessments is hence not applicable for studies where only ALL 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 examination.

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 examination. 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 MAS) but are clearly not leukemic 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 CR with incomplete blood count recovery (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 examination 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 2017 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 polymerase chain reaction (PCR) assays to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes or fusion transcripts (e.g. BCR-ABL (Philadelphia chromosome)). Current flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-4} (< 0.01%) bone marrow mononuclear cells (MNCs). 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, 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.

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

14.1.2.2 Baseline evaluation

The following baseline assessments are mandatory:

- 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)
- Cerebral spinal fluid cytology via LP for WBC, RBC and lymphoblast numbers (Section 14.1.2.1.3.1)
- CNS imaging (computed tomography scan or magnetic resonance imaging) or other appropriate assessment if clinical signs of CNS leukemia exist (Section 14.1.2.1.3.1)
- Physical examination 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 fluorescent *in situ* hybridization from bone marrow aspirate

For disease characterization at baseline, the most current assessments (bone marrow, blood count, CSF, physical examination, 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 examination 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 LP (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 LP will not be required unless it is clinically indicated by the presence of neurological 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 examination, bone marrow biopsy/aspirate (if needed) and LP (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 2017 v1) has defined a progressive disease (PD) category. In this document, PD is considered the same as "NR", which is consistent with Cheson et al (2003) guideline. The difference between PD and "NR" in ALL is not believed to be clinically meaningful.
- See Section 14.1.2.1.1 for details regarding assessing bone marrow response status.

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 > 1.0×10^9/L, and • Platelets > 100×10^9/L, and • Circulating blasts < 1% **Extramedullary disease** • No clinical evidence of extramedullary disease (by physical examination and central nervous system (CNS) symptom assessment) and • If additional assessments (e.g. cerebral spinal fluid assessment by lumbar puncture (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 ≤ 1.0×10^9/L, and/or • Platelets ≤ 100×10^9/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 (NR)	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 7 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 examination and CSF assessment by LP, is required at the first time a CR or CRi 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 examination 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.

CRs in patients with ALL have been observed to take place within 1 month after infusion with CTL019. The onset of CRs 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 examination 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 examination 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 examination. 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 NR can be assessed based on a partial evaluation (e.g. a relapse is assessed from blood alone). The assessment date for relapse or NR is calculated as the earliest date of all assessments that reveal a relapse or lack of response.

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; • central nervous system (CNS) disease; • other extramedullary disease.
Bone marrow biopsy / aspirate	Aspirate or biopsy; morphologic blast counts and minimal residual disease (MRD) assessment.
Blood response	Response status for platelets, neutrophils, morphologic blast counts; status of platelet and/or neutrophils transfusion.
Cerebral spinal fluid (CSF) assessment [1]	CSF lymphoblast, white blood cell (WBC), red blood cell (RBC)
Other CNS disease	CNS symptoms, confirmation of CNS disease via imaging or other methods (if applicable)
Extramedullary disease by physical examination	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.

14.1.3.3 Capturing overall response evaluation

Data monitoring reports will be prepared to identify Treating Physician's assessments which differ from calculated response based on the rules of this document. This discrepancy may be queried for clarification. However, the Treating Physician'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:

- Treating Physician 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 the Sponsor.

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. NR
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 examination and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi, as explained in Section 14.1.4.3.4.

The overall remission rate 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".

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 stem cell transplantation (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 (Committee for Medicinal Products for Human Use (CHMP) 2010). The handling of SCT for the calculation of DOR must be clearly specified in the protocol.

See also 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
- 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 NR 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 report and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of 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.

Using the draft Food and Drug Administration 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 duration of remission, event-free survival and relapse-free survival

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 (2) Date of next scheduled assessment	Event Event
C1	Relapse after **exactly one** missing assessment	(1) Date of relapse (2) Date of next scheduled assessment	Event Event
C2	Relapse after **two or more** missing assessments	(1) Date of last adequate assessment (2) Date of next scheduled assessment (3) Date of relapse	Censor Event Event
D	New anticancer therapy given (excluding stem cell transplantation (SCT))	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) Not applicable	Censor Censor Event Ignored
E	SCT	(1) Date of SCT (2) Not applicable (3) Date of SCT (4) Date of last adequate assessment prior to SCT	Censor Ignored Competing Risk Event Censor
F	Death due to reasons other than acute lymphoblastic leukemia (ALL) (for duration of remission (DOR) only)	(1) Date of death (2) Date of last adequate assessment	Competing Risk Event 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.

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, 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 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 report and analysis plan documentation.

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

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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, 2017 vl), Acute Lymphoblastic Leukemia. Available from:

...nccn.org/professionals/physician_gls/f_guidelines.asp

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

	Test	Result				
Hepatitis B	HBsAg	+	-	-	-	-
	HBcAb	Any	+	-	+	-
	HBsAb	Any	-	+	+	-
	Eligibility	Not Eligible	Eligible only if NAT for HBV DNA is negative	Eligible (NAT for HBV DNA can be performed for patients with LFTs abnormalities)	Eligible only if NAT for HBV DNA is negative	Eligible
Hepatitis C	HCV Ab	+	-			
	Eligibility	Eligible only if HCV RNA on blood by NAT is negative	Eligible			

NAT: Nucleic acid testing; LFTs: Liver function tests.

For indeterminate results where serology testing does not exclude active infection, blood sample for HBV DNA and/or HCV RNA by nucleic acid testing (NAT) should be obtained to confirm negative viral status (to exclude active viral infection / active viral replication).

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

HBcAb positive: As a standalone marker, it indicates 1) previous / resolved infection, 2) active ongoing or latent infection (acute ≤ 6 months if IgM anti-HBcAb) with risk for reactivation, or 3) false positivity. A positive HBcAb result (interpreted in the context of other HBV serology) should be followed by NAT for HBV DNA in blood.

If HBV DNA by NAT is detected, that indicates current active HBV infection. These subjects are not eligible for this trial.

If HBV DNA by NAT is not detected, that indicates either past / resolved HBV infection, or false HBcAb positivity. These subjects are eligible for this trial.

HBsAb positive: As a standalone marker, it indicates successful vaccination or previous infection that has been successfully resolved if the only positive finding. These subjects are eligible for this trial. In patients with LFTs abnormalities, NAT for HBV DNA can be performed.

HBsAg negative, HBcAb positive, HBsAb positive: Resolved or latent infection. For these patients, NAT for HBV DNA in blood should be performed.

If HBV DNA by NAT is detected, that indicates viral replication / reactivation of HBV infection. These subjects are not eligible for this trial.

If HBV DNA by NAT is not detected, that indicates resolved HBV infection. These subjects are eligible for this trial.

HCV Ab positive (reactive): Indicates 1) current active HCV infection, 2) past HCV infection that has resolved, or 3) false positivity.

A positive/reactive HCV Ab result should be followed by NAT for HCV RNA in blood.

If HCV RNA by NAT is detected, that indicates current active HCV infection. These subjects are not eligible for this trial.

If HCV RNA by NAT is not detected, that indicates either past, resolved HCV infection, or false HCV antibody positivity. These subjects are eligible for this trial.

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

14.3 Appendix 3: CTL019 modified data reporting – treatment and follow-up

This guidance is used to determine whether or not an AE, SAE, concomitant medication, or laboratory result has to be recorded in the CRF during the relevant study period. Before using this guidance, the investigator should determine whether or not an adverse event is serious using the criteria found in Section 8.1.2 of the protocol, and then use the applicable row of this guidance to determine whether or not that event is to be recorded in the CRF.

Table 14-4 Adverse event reporting

	Screening and Pre-treatment period (ICF to LD chemotherapy or pre-infusion visit)	**Treatment and Follow-up Period** (Starting from LD chemo/pre-infusion visit) **Through Month 12 Visit (end of study)**
AEs (non-serious and serious)	Modified: All clinical AEs grade ≥ 3 All SAEs and all deaths All laboratory abnormalities deemed clinically significant by the investigator All infections All AEs related to a study procedure (including related to leukapheresis) All AEs leading to study discontinuation	All AEs (i.e. non-serious AEs and SAEs) including all laboratory abnormalities deemed clinically significant by the investigator irrespective of causality Death due to disease progression with ≤ 30 days irrespective of causality and > 30 days with at least a possible relationship to CTL019

Table 14-5 Concomitant medication and laboratory reporting

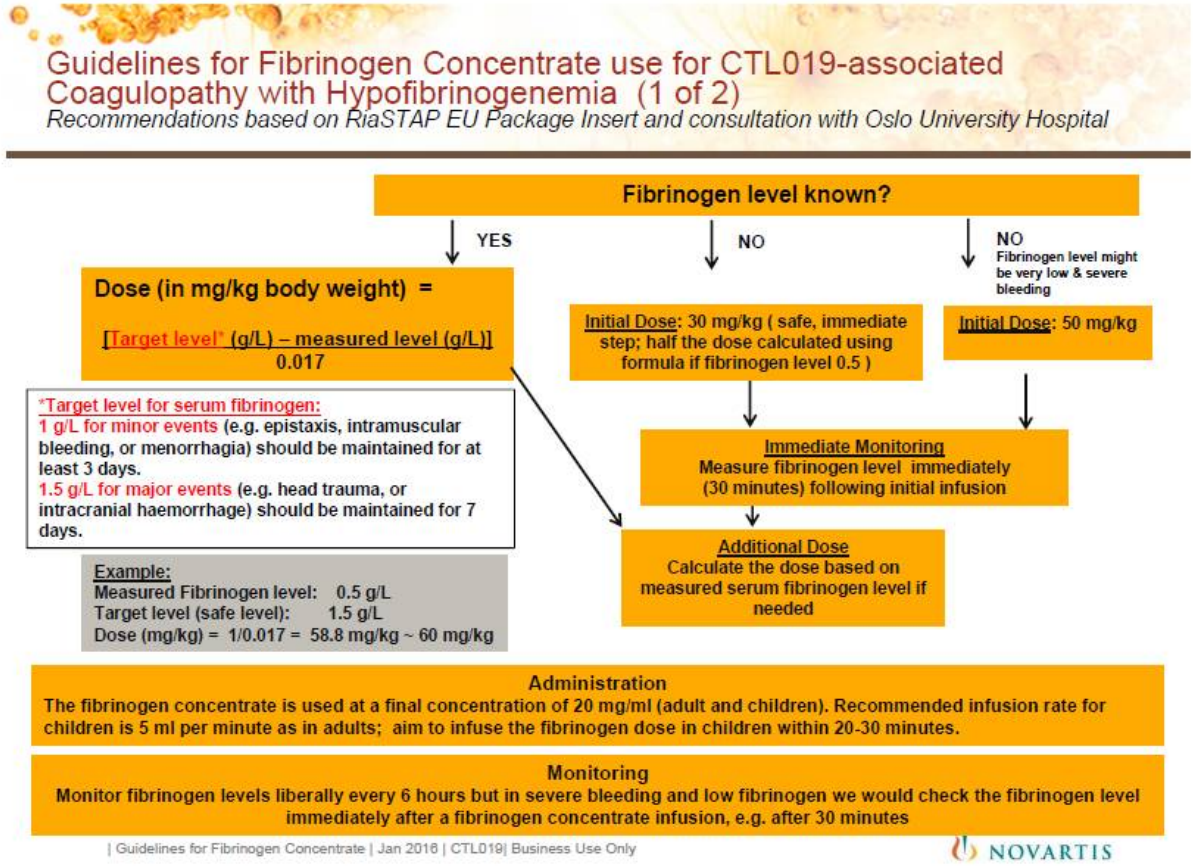
	Screening and Pre-treatment period **(ICF to LD chemo/pre-infusion visit)**	**Treatment and Follow-up Period** **(Starting from LD chemo/pre-infusion visit, through Month 12)**	
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**
Concomitant medications	Modified: **Drugs:** Record **all** of 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		All

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

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

14.4 Appendix 4: [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.



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.

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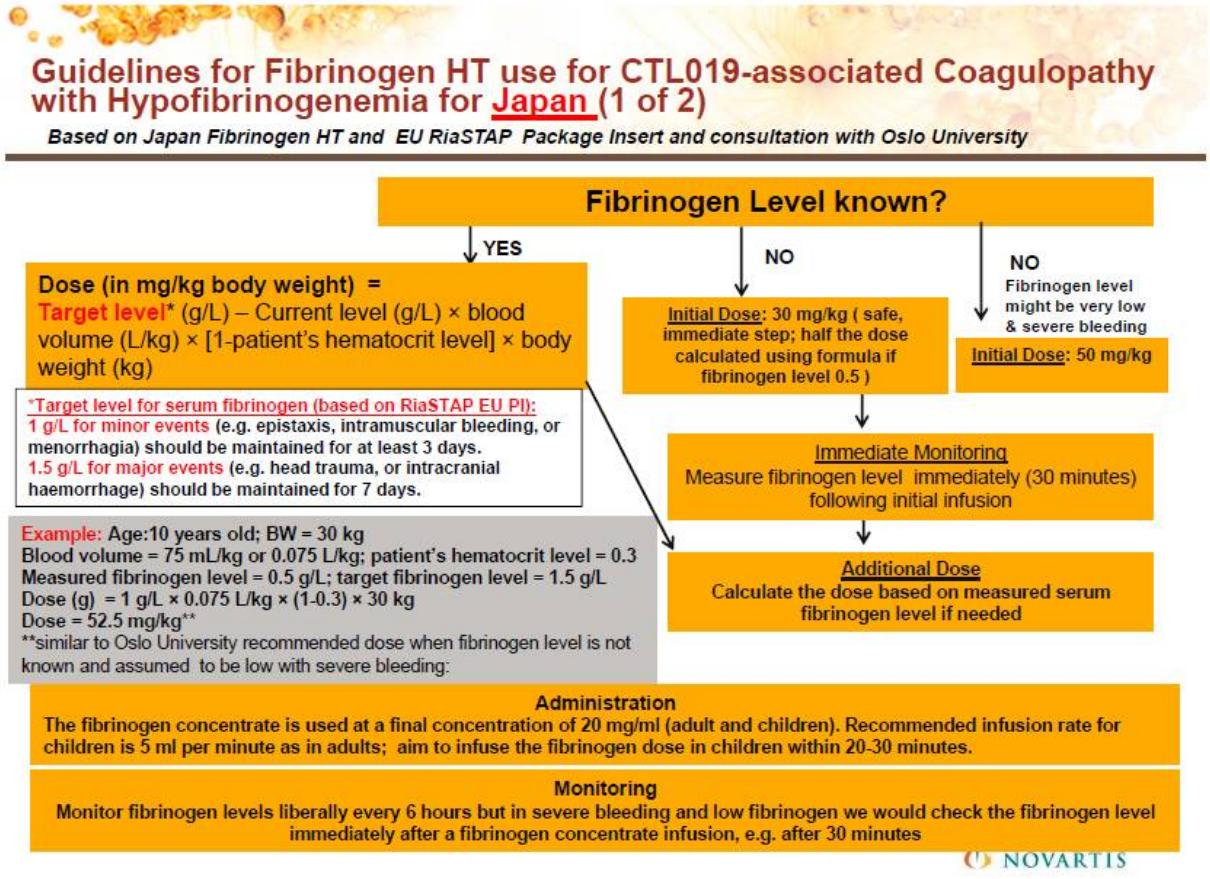
14.5 Appendix 5: [Japan Only: Guidelines for use of fibrinogen concentrate in CTL019- associated coagulopathy with hypofibrinogenemia]

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.



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.

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14.6 Appendix 6: Liver event and laboratory trigger definitions and follow-up requirements

Table 14-6 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 14-7 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	ALT, AST, TBL, indirect and direct bilirubin, albumin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring	
		Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	
> 3 × ULN and INR > 1.5		Discontinue the study treatment immediately (if applicable) Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., concomitant medication, medical history, lab) in the appropriate CRF	ALT, AST, 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	Investigator discretion

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

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

Criteria	Actions required	Follow-up monitoring

[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.

14.7 Appendix 7: Specific renal alert criteria and actions and event follow-up

Table 14-8 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

Table 14-9 Follow up of renal events

Assess, document and record in the appropriate CRF • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF.
Monitor patient regularly (frequency at investigator's discretion) until: • Event resolution: serum creatinine within 10% of baseline or PCR <1 g/g or albumin-creatinine ratio <300 mg/g) or • Event stabilization: serum creatinine level with ± 10% variability over last 6 months or PCR stabilization at a new level with ± 50% variability over last 6 months • Analysis of urine markers in samples collected over the course of the renal event