

Clinical Development

CTL019

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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

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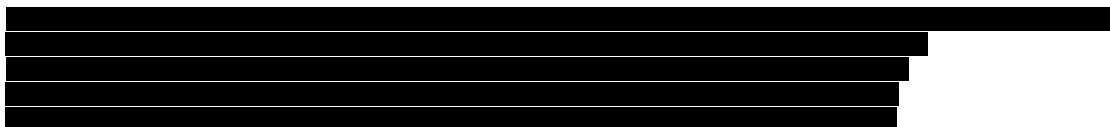
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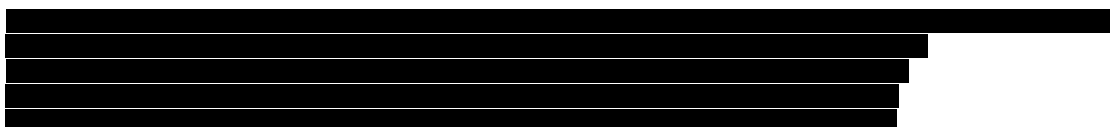
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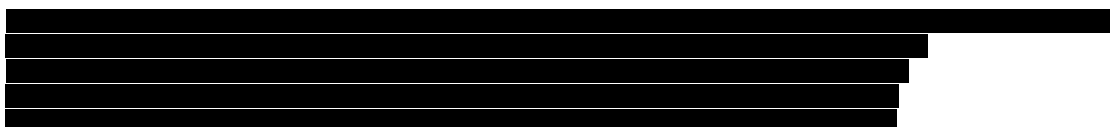
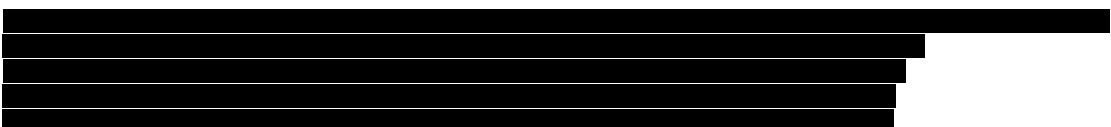


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List of abbreviations

AE	Adverse Event
4-1 BB	type 2 transmembrane glycoprotein belonging to the TNF superfamily, expressed on activated T Lymphocytes
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/SGPT
AML	Acute Myeloid Leukemia
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/SGOT
ATC	Anatomical Therapeutic Chemical
ATG	Anti-thymocyte globulin
AUC	Area Under the Curve
AUMC	Area under the first moment curve
B-ALL	B cell lineage acute lymphoblastic leukemia
BCR-ABL	Philadelphia Chromosome
BiPAP	Bilevel Positive Airway Pressure
BM	Bone Marrow
BMT	Bone Marrow Transplantation
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CAR	Chimeric Antigen Receptor
CBC	Complete Blood Count
CCGs	CRF Completion Guidelines
CD	Cluster of Differentiation
CD137	4-1BB costimulatory molecule
CFR	Code of Federal Regulations
CHOP	Children's Hospital of Philadelphia
CI	Confidence Interval
CIF	Cumulative Incidence Function
CLL	Chronic Lymphocytic Leukemia
C _{max}	Maximum concentration
CMC	Chemistry/ Manufacturing/ Control
CMO	Contract Manufacturing Facility Organization
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CR	Complete remission
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRi	Complete remission with incomplete blood count recovery
CRO	Contract Research Organization
CR _p	Complete remission with incomplete platelet recovery
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CRS	Cytokine Release Syndrome
CSF	Cerebral Spinal Fluid
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte
CTL019 cells	CD 19 redirected autologous T cells (also called CART19 T cells)
CVPF	Cell and Vaccine Production Facility
DLI	Donor Lymphocyte Infusion
DLBCL	Diffuse Large B Cell Lymphoma
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOR	Duration of Remission
EC	European Commission
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic Data Capture
EFS	Event Free Survival
EOS	End of Study
EOT	End of Treatment and Primary Follow-Up
FAB	Fragment Antigen Binding
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FISH	Fluorescent <i>in situ</i> hybridization
FL	Follicular Lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GMP	Good Manufacturing Practice
GU	Genitourinary
GVHD	Graft versus Host Disease
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLT	High level term
i.v.	Intravenous(ly)
IB	Investigator Brochure
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee



Ig	Immunoglobulin
IL	Interleukin
IL6R	Interleukin 6 receptor
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
ISBT	International Society of Blood Transfusion
IUD	Intrauterine Device
IVIG	Intravenous Immunoglobulin
KM	Kaplan Meier
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
LP	Lumbar Puncture
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
LVSF	Left Ventricular Shortening Fraction
MAP	Master Analysis Plan
MAS	Macrophage Activation Syndrome
MCHC	Mean Corpuscular Hemoglobin Concentration
MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Authorities
MHC	Major Histocompatibility Complex
MLL	Mixed-Lineage Leukemia
MNC	Mononuclear Cells
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
MUGA	Multiple Uptake Gated Acquisition
MYC	A regulator gene located on chromosome 8 that is disregulated via translocations in Burkitt's lymphoma/leukemia
NCCN	National Comprehensive Cancer Network
NE	Norepinephrine Equivalent
NHL	non-Hodgkin's lymphomas
NR	No Response
O ₂	Oxygen
ORR	Overall Remission Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PCR	Polymerase Chain Reaction
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PE	Physical examination
PGS-CRS	The Penn Grading Scale for Cytokine Release Syndrome
pH	Hydrogen ion concentration; a measure of the acidity or basicity of an aqueous solution
Ph+	Philadelphia Chromosome Positive
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PPS	Per-Protocol Set
PR	Partial Remission
PT	Preferred Term
PT	Prothrombin Time
aPTT	Activated Partial Thromboplastin Time
q-PCR	Quantitative Polymerase Chain Reaction
r/r	Relapsed or refractory
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RCL	Replication Competent Lentivirus
RDC	Remote Data Capture
REB	Research Ethics Board
RFS	Relapse Free Survival
SAE	Serious Adverse Event
SC	Steering Committee
scFv	Single chain Fv fragment of an antibody
SCID	Severe Combined Immunodeficiency
SCT	Stem Cell Transplantation
slg	Surface Immunoglobulin
SOC	System Organ Class
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SUSAR	Suspected Unexpected Serious Adverse Event
TCR	T Cell Receptor
TCR-zeta	Signaling domain found in the intracellular region of the TCR zeta, gamma and epsilon chains
TKI	Tyrosine Kinase Inhibitor
TLH	Trilineage Hematopoiesis
TLS	Tumor Lysis Syndrome
T _{max}	Time to peak concentration
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
UPenn	University of Pennsylvania
VASST	Vasopressin and Septic Shock Trial
V _H	Heavy Chain Variable Domain
V _L	Light Chain Variable Domain
VSV-G	Vesicular Stomatitis Virus, Glycoprotein
WBC	White Blood Cell

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
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 Novartis Morris Plains manufacturing facility.
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulations (CFR) 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number	A unique identifying number assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
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



Amendment 2

Amendment rationale

At the time of this protocol amendment, 9 sites have been initiated, 33 patients have been enrolled, and 27 patients have been treated.

The protocol is being amended to:

1. Ensure full alignment with the agreed binding measures detailed in the Pediatric Investigation Plan (PIP) opinion of the Paediatric Committee of the European Medicines Agency, issued on 20 March 2015, including the expansion of inclusion criteria to enroll patients with relapsed or refractory B-cell lymphoblastic lymphoma.
2. Address recommendations from EMA Scientific Advice letter on 25 April 2014
3. Transfer the trial sponsorship from University of Pennsylvania IND to Novartis IND.

Additional PK and cytokine sample time points were added to better define cell expansion and CRS, [REDACTED] that did not impact total sample collection requirements.

Testing for CMV and EBV is not required at screening per current guidelines for autologous blood product therapy.

Other changes have been instituted for purposes of clarity and feasibility based on experiences from ongoing trials as outlined below.

Key changes include:

1. The trial will be transferred under Novartis IND from UPenn IND. After the IND transfer, all CTL019 products will be manufactured according to the Novartis CMC process. An interim analysis is planned for patients who were treated with UPenn manufactured CTL109 product and have completed 6 months from study day 1 infusion or discontinued earlier. An α -spending function according to Lan-DeMets (O'Brien-Fleming) will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983).
2. Expand the inclusion criteria so that the trial can also enroll patients with relapsed or refractory B-cell lymphoblastic lymphoma, and add in the primary objective to assess ORR in lymphoblastic lymphoma patients too.
3. The final primary analysis will include at least 50 patients (both acute lymphoblastic leukemia and lymphoblastic lymphoma patients) treated using either UPenn CMC or Novartis CMC with at least 40 patients < 18 years. Sites will be notified once the cap of patients \geq 18 years is reached.
4. Clarification of primary endpoint to be assessed during the first 6 months after CTL019 administration.
5. Day 28 tumor assessment window changed from +/- 7 days to +/- 4 days
6. Additional analyses have been included to assess the response at Day 28 +/- 4 days, and the impact of baseline tumor burden on response.

[REDACTED]

7. Minimum number of manufactured CTL019 transduced cells for infusion has been removed.
8. Updated contraception guidelines for males and females of childbearing potential.

In addition, other changes have been instituted for purposes of clarity and further efficacy follow-up, as outlined below. Key changes include:

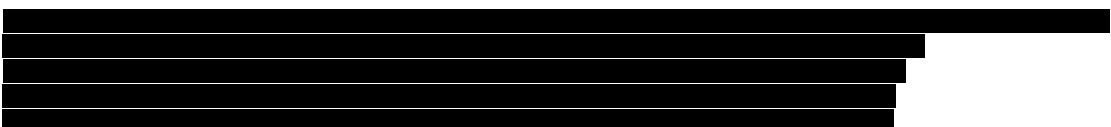
1. Extension of trial follow-up duration from 12 months to 60 months.
2. Clarifications to more accurately define the term “refractory ALL” in inclusion criteria #1. The two refractory populations now defined have equally poor prognosis at study enrollment and are not expected to negatively impact the population homogeneity.
3. Clarifications on adverse event reporting and apheresis collections

Changes to Protocol

1. Table 1-1: Clarity added for patient population on the trials
2. Section 1.2.1.2: Updated clinical experience section with currently available data. Clarification on correlation between administration of tocilizumab and CTL019 cell expansion.
3. Table 1-2: Removed and replaced with summary text
4. Table 2-1: Removed and replaced with summary text
5. Section 2.2: Replaced CVPF Penn manufacturing with Novartis manufacturing process will be used starting from Amendment 2
6. Section 2.3: Added “viable T” to dose.
7. Table 3-1: Objectives and endpoints updated to clarify primary endpoint to be assessed 6 months after CTL019 administration, addition of ORR assessment in lymphoblastic lymphoma patients, addition of other secondary objectives, [REDACTED]
8. Section 4.1: Study design diagram Extension of trial duration from 12 months to 60 months. Reference added.
9. Figure 4-1: Study design diagram updated with extension of trial duration from 12 months to 60 months.
10. Section 4.1.1: Clarity on guidelines for optimal apheresis collection
11. Section 4.1.1: Clarity on use of CTL019 manufactured cells if GVHD experienced after collection of apheresis product
12. Section 4.1.1: Removed reference to Manual of Procedures.
13. Section 4.2: Updated trial design to reflect extension of trial duration from 12 months to 60 months.
14. Section 4.3: Replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis.
15. Section 5.1: Addition of lymphoblastic lymphomas to patient population
16. Section 5.1: Clarification of European PIP required guidelines for primary analysis and capping of patients ≥ 18 years of age.

[REDACTED]

17. Section 5.2: Clarification on the definition of refractory ALL added to criteria # 1
18. Section 5.3: Criteria # 7 retired and replaced with criteria # 15 with extension of window for obtaining results within 8 weeks of screening
19. Section 5.3: Criteria # 8 retired and replaced with criteria # 16 with extension of window for obtaining results within 8 weeks of screening
20. Section 5.3: Criteria # 10 retired and replaced with criteria # 17 with additional Anti T-cell therapy guidance, and clarifications to testing time windows and chemotherapy in exclusion criteria.
21. Section 6.1.1.1: Clarification on timing of lymphodepleting chemotherapy before CTL019 infusion.
22. Section 6.1.1.2: Removed reference to University of Pennsylvania manufacturing facility and operational procedures. Anti T-cell Therapy details added. Clarifications on patient pre-infusion requirements. The number of tocilizumab doses required on site prior to CTL019 infusion changed to two doses. Clarification on which specific manual referenced. Minimum release dose criteria removed. Guidance on monitoring of patient temperature added.
23. Section 6.1.3: Number of tocilizumab doses required on site prior to CTL019 infusion changed to two doses.
24. Section 6.2.4.1: University of Pennsylvania Data Safety Monitoring Board (DSMB) replaced with Novartis Data Monitoring Committee (DMC).
25. Section 6.2.4.1.1: Replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis.
26. Section 6.2.4.2: CRS management algorithm to be followed by investigators.
27. Sections 6.2.4.2 & 6.2.4.3: Safety information added based on most current IB.
28. Figure 6-1: CRF Management Algorithm further clarified
29. Table 6-2: Adjustment of vasopressor doses corrected by weight.
30. Section 6.2.6: Modified concomitant medication reporting better defined; clarification on concomitant medication recording prior to screening. Clarification on administration of granulocyte colony stimulating factor (G-CSF).
31. Section 6.2.7: Anti T-cell Therapy guidance added. Clarifications added.
32. Section 6.3.1: Changed “the Sponsor” to “Novartis”.
33. Section 6.4: Clarification on which specific manual referenced, and changed “the person” to “personnel” to ensure alignment with manuals. Changed “Regulatory Sponsor” to “Novartis”. Clarification on which specific manual referenced.
34. Section 6.4.1: Added “viable T” and “transduced viable T” to dose.
35. Section 6.4.2: Clarification on which specific manual referenced.
36. Section 6.4.3: Clarifications on guidelines of product traceability between patient’s autologous apheresis and CTL019 product guidelines added. Clarification on which specific manuals referenced.
37. Section 6.4.3.2: Clarification on which specific manual referenced



38. Section 6.4.4: Clarification on which specific manuals referenced. Replaced “the Regulatory Sponsor” with “Novartis”
39. Section 7.1: Updated trial design to reflect extension of trial duration from 12 months to 60 months.
40. Figure 7-1: Added figure to reflect patient flow scenarios.
41. Table 7-1: Day 28 window changed from +/- 7 days to +/- 4 days.
42. Table 7-1: Enrollment window changed from “W-3 to D-8” to “W-8 to D-8”
43. Table 7-1: Pre-infusion window changed from “D-1” to “D-1 +1”
44. Table 7-1: Cytogenetics testing updated for relapsed patients
45. Table 7-1: Added collection timepoints of antineoplastic therapies treatment post CTL019 infusion
46. Table 7-1: Separated and added “Labs of Special Interest” from Chemistry panel
47. Table 7-1: Deleted “Viral Serology (CMV/ EBV)” testing
48. Table 7-1: Deleted “Flow Cytometry of bone marrow aspirate (B cell, tumor cell, CD19 assessment”
49. Table 7-1: Added MRD assessment by bone marrow aspirate by flow cytometry to include normal B and T cell counts and CD19 status
50. Table 7-1: Tumor cell assessment by flow cytometry of peripheral blood for clarity
51. Table 7-1: “Aspirate” added to lymph node or other involved tissue assessment
52. Table 7-1: Added Mediastinal disease assessment imaging for lymphoblastic lymphoma patients
53. Table 7-1: Added pregnancies and menstrual status
54. Table 7-1: CRS assessment by peripheral blood clarification
55. Table 7-1: Added CTL019 pharmacokinetics by flow cytometry (bone marrow aspirate)
56. [REDACTED]
57. [REDACTED]
58. [REDACTED]
59. [REDACTED]
60. Table 7-1: Added apheresis sample for correlative studies
61. Table 7-1: Added CTL019 cell product sample for correlative studies
62. Table 7-2: Added to reflect assessments performed from 12 month to 60 month period of Treatment and Primary Follow-Up.
63. Table 7-3: Added to reflect assessments performed during Secondary Follow-Up.
64. Section 7.1.1: Clarifications made throughout section. “at the time of screening” added to performance status assessment; Standard cytogenetics results clarified to be collected “at the time of most recent relapse. If not available, test must be performed at screening; “within 3 months of screening” added to donor chimerism; “Labs of special interest ([REDACTED] LDH, and fibrinogen)” added; HIV testing window updated and testing methodology updated; Viral serologies deleted; “test within 8 weeks of screening” added

[REDACTED]

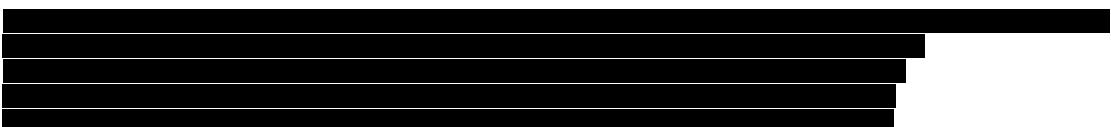
- to Hepatitis B/ C testing; T cell numbers added to bone marrow aspirate and biopsy and peripheral blood flow cytometry. Mononuclear cell isolation for genomic analyses added to bone marrow aspirate or biopsy. Mediastinal disease assessment added for relapsed or refractory B-cell lymphoblastic lymphoma.
65. 7.1.1.1: Clarification to operational impact of screening and enrollment requirements from transfer of IND from University of Pennsylvania to Novartis IND. Removal of third party review for confirmation of clinical eligibility.
 66. Section 7.1.2: Section updated with new visit windows and clarifications for pre-infusion criteria.
 67. Section 7.1.3: Section updated with new visit windows and other clarifications :. T cells added for flow cytometry; Day 28 window changed to +/- 4 days; “aspirate” added to lymph node assessment. Month 12, 15, 18, 21, 24, 30, 36, 42, 48, and 54 visit assessment details added.
 68. 7.1.3.1: Updated trial design to reflect extension of trial duration from 12 months to 60 months.
 69. 7.1.3.2: Section updated with criteria for premature patient withdrawal from Treatment and Primary Follow-Up
 70. [REDACTED]
 71. Section 7.1.4: Section updated and clarified.
 72. Section 7.1.4.1: Section added.
 73. Section 7.2.1: Updated with Lymphoblastic Lymphoma efficacy assessment reference.
 74. Table 7-2: Mandated collections added for 60 month extension of trial to peripheral blood , extramedullary disease assessment by physical exam, and flow cytometry of peripheral blood; Mediastinal disease assessment imagine for lymphoblastic lymphoma patients, T cells added for flow cytometry of peripheral blood; Deleted flow cytometry of bone marrow aspirate.
 75. Section 7.2.1.1: Updated with timepoints for extension of trial duration from 12 months to 60 months.
 76. Section 7.2.1.2: Updated with timepoints for extension of trial duration from 12 months to 60 months.
 77. Section 7.2.2: Further Tanner staging not required if patient classified as Tanner stage 5
 78. Section 7.2.2.4: Added Tanner Staging details.
 79. Table 7-4: Table updated for clarification. “B cell and T cell levels” added.
 80. [REDACTED]
 81. Section 7.2.3: Enrollment window changes from “W-3 to D-8” to “W-8 to D-8” and Day 28 window changed to +/- 4 days for all applicable tables.
 82. Table 7-6: Day 11 collection added; Collections added for extension of trial from 12 months to 60 months; clarification of collection of unscheduled samples.

[REDACTED]

83. Table 7-7: Table added for collection of CTL019 PK samples by flow cytometry of peripheral blood.
84. Table 7-9: Table added for collection of CTL019 pharmacokinetics by flow cytometry in bone marrow aspirate.
85. Table 7-11: Collections added for extension of trial from 12 months to 60 months; clarification of collection of unscheduled samples.
86. Table 7-11: Collections added for extension of trial from 12 months to 60 months; clarification of collection of unscheduled samples. Clarification added for primary follow up only.
87. Table 7-13: Table added for Tocilizumab CTL019 PK collection
88. Table 7-14: Table added for Anticytokine therapy (other than Tocilizumab) PK collection
89. Section 7.2.3.1: Section updated for clarification.
90. [REDACTED]
91. Section 7.2.4: Section added.
92. Section 8.1.2: Clarification added on adverse event reporting while patient simultaneously enrolled on CTL019B2206 and extension of trial from 12 months to 60 months.
93. Section 8.2.2: Clarification added on serious adverse event reporting while patient simultaneously enrolled on CTL019B2206 and extension of trial from 12 months to 60 months; "Regulatory Sponsor" replaced with "Novartis".
94. Section 8.2.3: Section deleted.
95. Section 8.4: "salpingotomy" corrected to "bilateral salpingectomy"; "the Regulatory Sponsor" replaced with "Novartis".
96. Section 8.6: Section deleted.
97. Section 8.7: Replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis and clarifications made
98. Section 8.8: Replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis.
99. Section 9: Clarifications added
100. Section 9.2: Replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis.
101. Section 9.4: Replaced "the Regulatory Sponsor" with "Novartis".
102. Section 10: Section updated with new population details and addition of formal interim analysis.
103. Section 10.1: Section updated based on new population
104. Section 10.1.6: Clarification added.
105. Section 10.2: Primary refractory definition clarified

[REDACTED]

106. Section 10.4 and subsections: Statistical analysis updates based on changes implemented in protocol
107. Section 10.5.2.2: Section updated
108. Section 10.5.2.3: Clarification added.
109. Section 10.5.2.4: Section removed (CR or CRi with MRD negative bone marrow)
110. Section 10.5.2.7: Section added
111. Section 10.5.2.8: Section added
112. Section 10.5.2.9: Section added
113. Section 10.5.3.7: Section added
114. Section 10.5.3.9: Section updated
115. Section 10.5.4: Section update
116. Table 10-4: Table updated with more details
117. Section 10.6.1: Section updated
118. Section 10.6.1.3: Section updated
119. Section 10.7: Section updated to include interim analysis.
120. Section 10.8: Section updated
121. Section 10.6.4: Patient reported outcome section removed and moved to Section 10.5.2.7
122. Section 10.8: Section updated
123. Section 11.2: Clarifications made for updated bodied and replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis.
124. Section 11.3: Clarifications made; replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis.
125. Section 11.4 and 11.5: Replaced “the Regulatory Sponsor” with “Novartis”.
126. Section 11.6: Replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis
127. Section 11.7: Replaced “the Funding Sponsor” with “Novartis”
128. Section 11.8: Replaced “the Regulatory Sponsor” with “Novartis”.
129. Section 12: Replaced “the Regulatory Sponsor” with “Novartis”.
130. Section 12.1: Clarifications made for updated bodied and replaced reference to University of Pennsylvania regulatory and safety bodies with Novartis
131. Section 13: References added
132. Section 14.1 Appendix 1: Updated
133. Section 14.2 Appendix 2: Lymphoblastic lymphoma assessment guidelines added
134. Section 14.3 Appendix 3: clarifications made
135. Section 14.4 Appendix 4: CTL019 Modified Safety Reporting guidelines added



IRB/IEC

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

The changes described in this amended protocol require IRB/EC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1

Amendment rationale

This protocol amendment was finalized under the UPenn IND and therefore, a rationale was not included at the time. Therefore, at the time of transitioning the trial to Novartis IND, it has been retrospectively added.

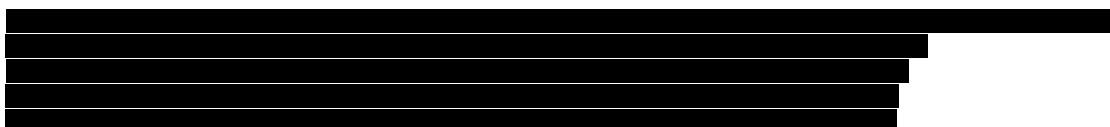
At the time of this protocol amendment, no sites had been initiated and first patient first visit (FPFV) had not occurred. All sites are to be initiated with the current protocol amendment.

The protocol was being amended in order to include additional safety information and includes Health Authority feedback regarding reporting of SAEs including CRS and deaths, updating CTL019 dosing, staggered-enrollment design, follow-up time required after a live birth, influenza testing 10 days prior to infusion, general toxicity management, and modified Serious Adverse Event (SAE) and Adverse Event (AE) reporting.

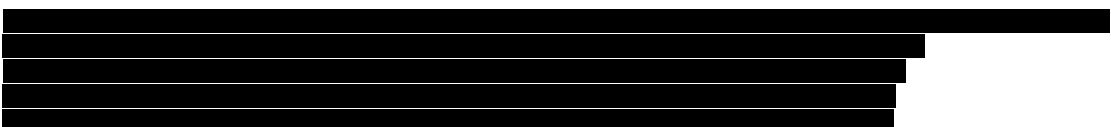


Protocol summary:

Protocol number	CCTL019B2205J
Title	A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia
Brief title	Study of efficacy and safety of CTL019 in pediatric ALL patients
Sponsor and Clinical Phase	Novartis Phase II Multicenter
Investigation type	Biological
Study type	Interventional
Purpose and rationale	<p>Outcome remains poor for patients with second or greater relapse or refractory (r/r) pediatric B-cell ALL and Lymphoblastic Lymphoma. Treatment options for r/r B-cell ALL and Lymphoblastic Lymphoma include further treatment with salvage chemotherapy, allogeneic SCT or supportive care. Therapy in this population is not curative with an overall survival of 3 to 6 months.</p> <p>CD19 has emerged as an attractive therapeutic target because it is widely expressed on normal and malignant B-cells throughout B-cell maturation but not on pluripotent stem cells or non-B-cell tissues. The development of chimeric antigen receptor (CAR) T cells to target CD19+ cells (CART19 or CTL019) provides an innovative new approach to these malignancies. This approach involves autologous patient-derived T cells that are genetically modified ex vivo via lentiviral transduction to express a CD19 antigen recognition domain attached to intracellular signaling domains that mediate T-cell activation in a MHC independent manner. Anti-tumor efficacy has been seen in r/r adult and pediatric ALL and in r/r CLL.</p>
Primary Objective(s) and Key Secondary Objective	<p>To evaluate the efficacy of CTL019 therapy in acute lymphoblastic leukemia patients as measured by overall remission rate (ORR), 6 months after CTL019 administration, which includes Complete Remission (CR) and CR with incomplete blood count recovery (CRi) as determined by independent review committee (IRC) assessment.</p> <p>ORR in Lymphoblastic Lymphoma patients will be evaluated separately using local investigator's assessment.</p>
Secondary Objectives	<p>These objectives will be assessed in the acute lymphoblastic leukemia patients and separately in the lymphoblastic lymphoma patients.</p> <p>Objective 1: To evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment</p> <p>Objective 2: To evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment</p> <p>Objective 3: To evaluate the duration of remission (DOR).</p> <p>Objective 4: To evaluate the quality of response by assessing the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a minimal residual disease (MRD) negative bone marrow 6 months after CTL019 infusion and at D28 by central analysis.</p> <p>Objective 5: To evaluate the relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS)</p> <p>Objective 6: Evaluate the response at Day 28+/-4 days</p> <p>Objective 7: To evaluate the impact of baseline tumor burden on response</p> <p>Objective 8: To evaluate the safety of CTL019 therapy as measured by type, frequency and severity of adverse events and laboratory abnormalities</p> <p>Objective 9: To characterize the in vivo cellular pharmacokinetic (PK) profile (levels, persistence, trafficking) of CTL019 cells in target tissues (blood, bone marrow, and other tissues if available)</p> <p>Objective 10: To describe the prevalence and incidence of immunogenicity to CTL019</p> <p>Objective 11: To describe the profile of soluble immune factors that may be key to cytokine</p>



	<p>release syndrome</p> <p>Objective 12: To describe the levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion</p>																							
Study design	<p>This is a single arm, open-label, multi-center, phase II study to determine the efficacy and safety of CTL019 in pediatric patients with r/r B-cell ALL and lymphoblastic lymphoma. The study will have the following sequential phases: Screening, Pre-Treatment (Cell Product Preparation & Lymphodepleting Chemotherapy), Treatment and Primary Follow-up, Secondary Follow-up (if applicable) and Survival Follow-up. The total duration of the study is 5 years from CTL019 cell infusion. After CTL019 infusion, efficacy will be assessed monthly for the first 6 months, quarterly up to 2 years, and semi-annually afterwards up to 5 years, or until patient relapse. Safety will be assessed throughout the study. A post-study follow-up for lentiviral vector safety will continue under a separate destination protocol for 15 years post infusion per health authority guidelines. An interim analysis is planned when all acute lymphoblastic leukemia patients who were enrolled and CTL019 manufactured according to the UPenn manufacturing process have completed 6 months from study day 1 infusion or discontinues earlier.</p>																							
Population	<p>The target population is comprised of pediatric patients with B-cell ALL and Lymphoblastic Lymphoma who are primary refractory, chemo-refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT. Approximately 67 patients will be enrolled to allow 50 total patients to be treated which will consist of patients with relapsed or refractory acute lymphoblastic leukemia and/or lymphoblastic lymphoma age 3 at the time of screening to age 21 at the time of initial diagnosis.</p> <p>In order to satisfy European PIP requirement, at least 40 patients <18 years of age will be treated at the time of primary analysis. Therefore, <u>no more than 10 patients ≥18 years of age will be treated</u>. Sites will be notified when this age cap is reached.</p> <p>The number of acute lymphoblastic leukemia and lymphoblastic lymphoma patients to be treated respectively will be based on the actual recruitment of the two populations. It is anticipated that the lymphoblastic lymphoma population is small and will represent less than 10% of the entire population. Therefore with 50 patients treated in the study, it is assumed that 45 acute lymphoblastic leukemia patients will be treated.</p>																							
Inclusion criteria	<ol style="list-style-type: none"> 1. [Retired from UPenn protocol version 2.0] 2. For relapsed patients, documentation of CD19 tumor expression in bone marrow or peripheral blood by flow cytometry within 3 months of study entry 3. Adequate organ function defined as: <ol style="list-style-type: none"> a. Renal function defined as: <ol style="list-style-type: none"> i. Calculated creatinine clearance or radioisotope Glomerular Filtration Rate (GFR) > 60 mL/min/1.73 m², OR ii. A serum creatinine based on age/gender as follows: <table border="1" style="margin-left: 40px;"> <thead> <tr> <th rowspan="2">Age</th> <th colspan="2">Maximum Serum Creatinine (mg/dL)</th> </tr> <tr> <th>Male</th> <th>Female</th> </tr> </thead> <tbody> <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> </tbody> </table> b. Alanine Aminotransferase (ALT) ≤ 5 times the upper limit of normal (ULN) for age c. Bilirubin < 2.0 mg/dL d. Must have a minimum level of pulmonary reserve defined as ≤Grade 1 dyspnea and pulse oxygenation > 91% on room air e. Left Ventricular Shortening Fraction (LVSF) ≥ 28% confirmed by echocardiogram, or Left Ventricular Ejection Fraction (LVEF) ≥ 45% confirmed by echocardiogram or MUGA 4. Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening 	Age	Maximum Serum Creatinine (mg/dL)		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
Age	Maximum Serum Creatinine (mg/dL)																							
	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																						



	<p>5. Life expectancy > 12 weeks 6. [Retired from UPenn protocol version 2.0]. 7. Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50 at screening 8. Signed written informed consent and assent forms if applicable must be obtained prior to any study procedures 9. Once all other eligibility criteria are confirmed, must have an apheresis product of non-mobilized cells received and accepted by the manufacturing site. 10. Relapsed or refractory pediatric B-cell Acute Lymphoblastic Leukemia or B-cell Lymphoblastic Lymphoma, AND a. 2nd or greater BM relapse OR b. Any BM relapse after allogeneic SCT and must be > 6 months from SCT at the time of CTL019 infusion 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 relapse leukemia OR d. Patients with Ph+ ALL are eligible if they are intolerant to or have failed two lines of TKI therapy, or if TKI therapy is contraindicated OR e. Ineligible for allogeneic SCT because of: i. Comorbid disease ii. Other contraindications to allogeneic SCT conditioning regimen iii. Lack of suitable donor iv. Prior SCT v. Declines allogeneic SCT as a therapeutic option after documented discussion, including expected outcomes, about the role of SCT with a BMT physician not part of the study team 11. Age 3 at the time of screening to age 21 at the time of initial diagnosis.</p>
<p>Exclusion criteria</p>	<p>1. Isolated extra-medullary disease relapse 2. Patients with concomitant genetic syndrome: 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 (slg) positive and kappa or lambda restricted positivity] ALL, with FAB L3 morphology and /or a MYC translocation) 4. Prior malignancy, except carcinoma <i>in situ</i> of the skin or cervix treated with curative intent and with no evidence of active disease 5. Prior treatment with gene therapy product 6. Treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy 7. [Retired from UPenn protocol version 2.0] 8. [Retired from UPenn protocol version 2.0] 9. Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD) 10. [Retired from UPenn protocol version 2.0] 11. Active CNS involvement by malignancy, defined as CNS-3 per National Comprehensive Cancer Network (NCCN) guidelines. Note: Patients with history of CNS disease that has been effectively treated will be eligible. 12. Patient has participated in an investigational research study using an investigational agent within the last 30 days prior to screening 13. Pregnant or nursing (lactating) women. NOTE: female study participants of reproductive potential must have a negative serum or urine pregnancy test performed within 48 hours before infusion 14. [Retired from UPenn protocol version 2.0] 15. Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening 16. HIV positive test within 8 weeks of screening 17. The following medications are excluded: a. Steroids: Therapeutic doses of steroids must be stopped > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: < 12 mg/m2/day hydrocortisone or equivalent</p>



	<p>b. Allogeneic cellular therapy: Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion</p> <p>c. GVHD therapies: Any drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate mofetil, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-TNF, anti-IL6 or anti-IL6R)</p> <p>d. Chemotherapy: The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: hydroxyurea, vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m², cytosine arabinoside < 100 mg/m²/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/m², anthracyclines, cyclophosphamide), excluding the required lymphodepleting chemotherapy drugs Pegylated- asparaginase must be stopped >4 weeks prior to CTL019 infusion</p> <p>e. CNS disease prophylaxis: i. CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)</p> <p>f. Anti T-cell Therapy: Administration of any T cell lytic or toxic agent (e.g. alemtuzumab) prior to CTL019 is strongly discouraged 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 Novartis, consider consultation with a pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.</p> <p>18. Women regardless of age that may have child-bearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants, unless they are using highly effective methods of contraception for a period of 1 year after the CTL019 infusion). Women are to continue contraception until CAR cells are no longer present in the blood by PCR. Highly effective contraception methods include:</p> <ul style="list-style-type: none">a. 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)b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessmentc. Male sterilization (at least 6 months prior to screening). For female participants on the study the vasectomized male partner should be the sole partner for that patientd. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraceptione. Use of intrauterine devices (IUDs) are excluded due to increased risks of infection and bleeding in this populationf. In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment <p>Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months (i.e. have had no menses) or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception. Women who are not yet of reproductive potential are to agree to use acceptable forms of contraception when they reach reproductive potential if within 1 year of CTL019 or if CAR cells are present in the blood by PCR. Acceptable documentation includes written or oral documentation communicated by clinician or clinician's staff of one of the following:</p> <ul style="list-style-type: none">a. Demographics show age <11b. Physical examination indicates Tanner Stage 1c. Physician report/letterd. Operative report or other source documentation in the patient record
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	<p>e. Discharge summary</p> <p>f. Follicle stimulating hormone measurement elevated into the menopausal range</p>
Investigational and reference therapy	A dose of CTL019 transduced cells will consist of a single infusion of 2 to 5 x 10 ⁶ CTL019 transduced viable T cells/kg with a maximum dose of 2.5 x 10 ⁸ CTL019 transduced viable T cells (non-weight adjusted).
Efficacy assessments	<p>Primary: Overall Response Rate (ORR), 6 months after CTL019 administration, which includes Complete Remission (CR) and Complete Remission with Incomplete Blood Count Recovery (CRi), as determined by assessments of peripheral blood, bone marrow, CNS symptoms, physical exam (PE) and CSF. The primary endpoint will be based on the IRC assessment for acute lymphoblastic leukemia patients, and based on local investigator's assessment for acute lymphoblastic lymphoma patients. The local investigator's assessed results will be used for sensitivity analysis for acute lymphoblastic leukemia patients.</p> <p>Secondary: Patients with CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment, patients who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment, Minimal residual disease, duration of remission, relapse-free survival, event-free survival, and overall survival</p>
Safety assessments	<p>Adverse events and laboratory abnormalities (type, frequency and severity)</p> <p>Immunogenicity assessments</p> <p>a. prevalence of immunogenicity against CTL019 (pre-existing), both humoral and cellular</p> <p>b. incidence of immunogenicity against CTL019, both humoral and cellular</p> <p>c. proportion of patients with transient anti-CTL019 antibody assay titers</p> <p>d. proportion of patients with sustained anti-CTL019 antibody assay titers</p>
Other assessments	<p>Pharmacokinetic assessments planned for this trial include:</p> <ul style="list-style-type: none"> ● Detection of CTL019 transgene levels in blood, bone marrow and CSF (if available) by q-PCR. ● Expression of CTL019 detected by flow cytometry in blood and bone marrow ● Maximum Concentration (C_{max}), Time of Peak Concentration (T_{max}), Area Under the Curve (AUCs) and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF (if available). ● Maximum extent of expansion of CTL019 in blood ● Persistence of CTL019 in blood, bone marrow and CSF (if available)
Data analysis	<p>Primary endpoints:</p> <ul style="list-style-type: none"> ● The primary analysis will be carried out after 50 treated patients have completed at least 6 months of follow-up or have discontinued due to any reason. Updated efficacy and safety data will be reported after patients have been followed for a total of 60 months within the study protocol. ● The primary efficacy endpoint, ORR will be assessed by IRC for Acute Lymphoblastic Leukemia patients and by local investigator's assessment for Lymphoblastic Lymphoma patients in the full analysis set (FAS). The primary efficacy analysis will be based on statistical testing in acute lymphoblastic leukemia patients, descriptive analysis in lymphoblastic lymphoma patients, and descriptive analysis in all patients combined. ● The primary efficacy analysis in acute lymphoblastic leukemia patients will be performed

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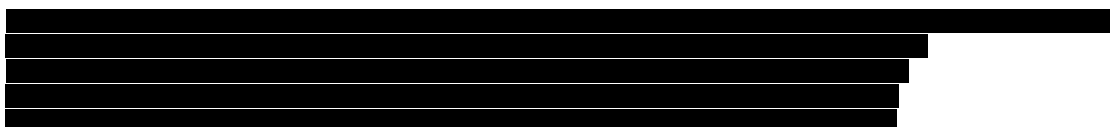
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

	<p>by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that the ORR is greater than 20% at overall one-sided 2.5% level of significance, powered for ORR = 45%. The ORR will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets. The study will be considered successful if the lower bound of the 2-sided exact confidence interval for ORR is greater than 20%, so that the null hypothesis that the ORR is less than or equal to 20% can be rejected. Sensitivity analyses will be performed on the Enrolled Set, the per-protocol set (PPS) and with all patients who satisfy all clinical eligibility criteria (defined as all inclusion/exclusion criteria except that which pertains to the apheresis product) using the same method as described above.</p> <p>Secondary endpoints:</p> <ul style="list-style-type: none">• Analysis of secondary or exploratory endpoints will be descriptive and may include summary statistics such as means, standard deviations, 95% confidence intervals, if applicable. Cumulative Incidence Functions (CIF), Kaplan-Meier curves and median time to event will be presented for time-to-event variables (DOR, RFS, EFS and OS), if appropriate. <p>Interim Analysis:</p> <ul style="list-style-type: none">• An interim analysis is planned when all acute lymphoblastic leukemia patients who were enrolled and CTL019 manufactured according to the UPenn manufacturing process have completed 6 months from study day 1 infusion or discontinued earlier. Approximately 30 patients will be included in the interim analysis. An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in East 6.1, will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983). If the interim analysis is performed exactly with 30 patients, the lower bound of the 2-sided 98.79% exact CI of the ORR will need to be greater than 20% to declare statistical significance <p>Sample size:</p> <ul style="list-style-type: none">• In a previous study of clofarabine in pediatric patients with r/r B-cell ALL who have had 2 or more prior regimens, the reported ORR was 20%. Based on the null hypothesis of ORR \leq 20% and alternative hypothesis of ORR = 45%, 50 patients in the FAS will provide 95% power to demonstrate statistical significance using a 2-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary at one-sided 2.5% level of significance. Assuming 20% to 25% enrolled patients will not be infused due to reasons such as product manufacturing issues, worsening of patient's condition, etc., at least 63 to 67 patients need to be enrolled respectively to ensure 50 acute lymphoblastic leukemia or lymphoblastic lymphoma patients are treated using either UPenn or Novartis CMC process and hence will be used for the primary analysis
Key words	Relapsed/refractory ALL or Lymphoblastic Lymphoma, relapsed ALL, post allogeneic SCT, CTL019



1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

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

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

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

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

1.2.1 Overview of CTL019

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



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

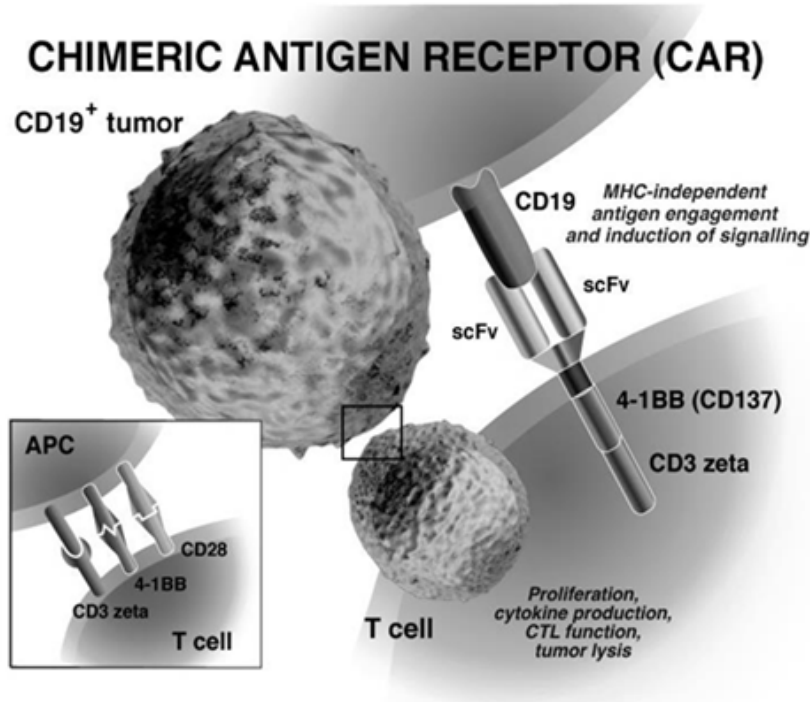
A very promising potential target antigen for B cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors ([Sadelain et al 2003](#), [Brentjens et al 2010](#), [Porter et al 2011](#)). CD19 is not expressed on hematopoietic stem cells or non-B cell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

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

CTL019 (CART-19) is an adoptive cellular immunotherapy that uses the autologous peripheral blood T cells that have been genetically modified *ex vivo* to target CD19 on the surface of B cells. As shown in [Figure 1-1](#), the CAR approach uses genetically programmed lymphocytes 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 (V_H) and light chain variable domain (V_L) chains joined by a peptide linker of about 15 residues in length ([Mullaney et al 2001](#)).



Figure 1-1 CTL019 chimeric antigen receptor design



Early results from ongoing clinical trials of CTL019 in r/r CLL and r/r ALL have shown promising and durable anti-tumor efficacy (Porter et al 2011, Grupp et al 2013, Maude 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.

1.2.1.1 Non-clinical experience

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



1.2.1.2 Clinical experience

For a summary of ongoing human studies with CTL019 (patients treated, disease indication, CTL019 dosing), please refer to the Investigator Brochure.

Initial dosing in adults and children, for safety reasons, used a split infusion schedule of escalating doses. However, the majority of patients in the two phase I studies received CTL019 as a single one time infusion or two sequential infusions due to the onset of fevers and other clinical events precluding further infusions. For pediatric patients, cells are dosed per kg body weight where dosing in adults does not consider body weight.

Safety

Pediatric r/r Acute Lymphoblastic Leukemia

Toxicities seen in pediatric r/r ALL patients include expected chemotherapy related adverse events (AE) and CTL019 related events of tumor lysis syndrome (TLS) and CRS/macrophage activation syndrome (MAS) (Grupp et al 2013, Maude 2014). TLS and CRS/MAS in ALL patients typically occurred within days to a week following CTL019 infusion and correlated with peak *in vivo* CTL019 cell expansion. TLS complications were managed as per standard of care including prophylactic allopurinol (in patients with elevated uric acid or high tumor burden) and fluids, and rasburicase as needed. CRS/MAS has been managed in pediatric ALL patients with supportive care and when needed, tocilizumab (anti-IL-6 receptor monoclonal antibody) therapy. Since CRS mechanistically is believed to be a required part of the antitumor mechanism of *in vivo* CTL019 cell expansion and tumor killing, tocilizumab was administered for CRS only after symptoms became moderate or severe. This included worsening respiratory distress, pulmonary infiltrates, increasing oxygen requirement (defined as high-flow oxygen and/or need for mechanical ventilation), hemodynamic instability despite intravenous fluids and moderate/high dose vasopressor support, and/or rapid clinical deterioration. Preliminary data supports that management with tocilizumab does not appear to diminish CTL019 cell expansion, therefore tocilizumab should be administered for CRS when symptoms warrant treatment per the CRS management algorithm (Figure 6-1). Steroids following CTL019 infusion were avoided and given only under life threatening situations due to their known lympholytic effects. Clinical responses do not appear to correlate prior relapsed or refractory status of the patient. CRS severity appears to correlate with pre-infusion tumor burden in pediatric ALL but not with CTL019 transduced cell numbers within the range of cell doses studied. More severe CRS is associated with earlier clinical onset of CRS related symptoms in pediatric r/r ALL patients. Refer to Section 6.2.4.2 for guidance related to CRS management and the [Investigator Brochure] for additional safety information.

As of May 2015 51 pediatric r/r ALL patients were treated on the CHP959 Phase I study with either one, two, or three doses of CTL019 with split dosing (10%, 30%, 60%). The age range of patients was 4 to 22 years. CRS of variable severity was seen in 46 pediatric patients out of the 51. Of the 46 patients with CRS, 24 patients had Grade 3 or 4 CRS (47.1%). Median time to CRS onset was three days (day 1 to 11) and median time to CRS resolution was 11 days (day 6 to 24). CRS that developed into severe Grade 4 (defined as hypotension requiring the



use of two or more vasopressors or respiratory failure requiring mechanical ventilation) had an initial onset at median of day 2 after infusion, whereas CRS that did not develop into Grade 4 (non-severe) had an initial onset at a median of day 5 after infusion. Fifteen patients (33%) required tocilizumab (one to three doses) in addition to supportive care for management of CRS which resulted in rapid defervescence and stabilization of blood pressure, with improvement (weaning from vasopressor support) over a period of 1 to 3 days. Nineteen (42%) patients required admission to the intensive care unit (ICU) with 5 patients requiring high dose vasopressor support and 6 patients requiring mechanical ventilation. Disseminated intravascular coagulation requiring blood product support was seen in 5 patients and reversible encephalopathy was seen in 16 patients. CRS seen in pediatric patients was manageable with supportive care, and, when needed, tocilizumab. All pediatric patients recovered fully with complete reversal of symptoms and a normalization of laboratory results. Patients achieving a CR also experienced B-cell aplasia and hypogammaglobulinemia, which was supported with periodic intravenous immune globulin infusions as per local guidelines. GVHD was not seen in the patients who had previously undergone an allogeneic SCT with known donor chimerism. No acute fatalities were observed in this phase I study.

[Maude et al \(2014\)](#) reported that 13/30 CTL019 treated patients (25 pediatric and 5 adult) in the Phase I trials as of March 2014 had neurologic toxic effects, which ranged from delirium during the period of high fevers to global encephalopathy with one or more of the following: aphasia, confusion, delirium, and hallucinations. Six patients had delayed encephalopathy that occurred after high fevers had resolved and was independent of the severity of the CRS and whether the patient had received prior tocilizumab therapy. Symptoms were self-limiting (lasting 2 to 3 days and resolving over 2 to 3 days), and they resolved fully without further intervention or apparent long-term sequelae. One patient with encephalopathy had two seizures that may have been caused by concomitant electrolyte abnormalities. Several patients had normal computed tomographic or magnetic resonance imaging of the head and lumbar puncture that was negative for infection or leukemia.

Responding CLL and ALL patients demonstrated detectable and prolonged persistence of CTL019 transduced cells in the setting of CR; over 2 years in one ALL patient, and over 4 years in two CLL patients ([Porter 2011](#), [Grupp 2013](#), [Maude 2014](#)).

Pediatric r/r Lymphoblastic Lymphoma

Patients with relapse/refractory B-cell lymphoblastic lymphoma are a very rare patient population with no curative therapies other than allogeneic SCT. To date, patients with B cell lymphoblastic lymphoma have yet to be treated with CTL019.

Adult r/r ALL

As of May 2015, 21 adult r/r ALL patients have been treated on a phase I trial (UPCC04409 protocol, NCT01029366) or phase II trial (UPCC21413 protocol, NCT02030847) under the Penn IND. The age range is 20 to 71 years. CRS was seen in 20 of 21 patients. Seventeen patients (81%) had Grade 3 or 4 CRS and 17 (85%) of these patients required anti-cytokine therapy with tocilizumab.



The phase II adult r/r ALL UPCC21413 trial utilized a single infusion of a higher dose of CTL019 cells. Among the first six patients treated, three deaths were attributable to Grade 5 refractory CRS in the setting of significant concomitant infections. The subsequent six patients on this trial were then treated with a reduced cell dose of CTL019. Two early deaths out of these six subsequent patients were seen with the lower dose of CTL019 cells, however, CRS in these two cases was deemed not to be refractory to intervention. The cause of death was cerebral hemorrhage in one patient and sepsis in the other patient. The last three patients treated with the same reduced cell dose of CTL019 using a split dosing model. No early deaths were observed.

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

Efficacy

As of May 2015, of the 51 r/r pediatric ALL patients treated in the CHP959 Phase I study, 46/51 (90%) achieved complete remission (CR or CRi). Similar response rates were seen in patients with or without prior allogeneic stem cell transplant. All responding patients developed B-cell aplasia. The administered dose range per kg was 1.0×10^6 to 17.3×10^6 transduced CTL019 cells/kg. The total transduced CTL019 cells administered was 0.3×10^8 to 9.1×10^8 CTL019 cells.

2 Rationale

2.1 Study rationale and purpose

Outcome remains poor for patients with r/r pediatric B-cell lineage acute lymphoblastic leukemia (B-cell ALL). Treatment options for r/r B-cell ALL include further treatment with salvage chemotherapy, second allogeneic stem cell transplantation (SCT) or supportive care. Therapy in this population is not curative with an overall survival of 3 to 6 months (Smith 2010, Tallen 2010, Martin 2012, Ko 2010, Duval 2010, Oudot 2008). As an example, clofarabine was approved by the Food and Drug Administration (FDA) for the treatment of pediatric patients with r/r ALL after at least 2 prior therapeutic regimens. The overall remission rates were 30% for ALL and 38% for Acute Myeloid Leukemia (AML) in Phase I studies (Jeha et al 2004); 30% (20% CR or complete remission with incomplete platelet recovery [CR_p] and 10% Partial Remission [PR]) for ALL and 26% for AML in Phase II studies (Jeha et al 2006). The median duration of remission for patients with ALL who achieved at least a partial remission was 9.7 weeks (range 7 to 335 days) in the Phase II study.

CD19 has emerged as an attractive therapeutic target because it is widely expressed on normal and malignant B-cells throughout B-cell maturation but not on pluripotent stem cells or non-



B-cell tissues. The development of CAR T cells to target CD19+ cells (CART19 or CTL019) provides an innovative new approach to these malignancies. This approach involves recipient-derived T cells that are genetically modified *ex vivo* via lentiviral transduction to express a CD19 antigen recognition domain attached to intracellular signaling domains that mediate T-cell activation in an MHC independent manner. Encouraging anti-tumor efficacy has been seen in r/r adult and pediatric ALL and in r/r CLL.

2.2 Rationale for the study design

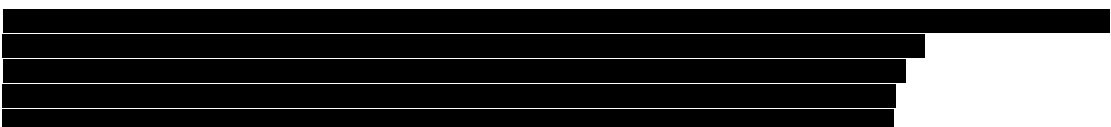
This is a single arm, multi-center, phase II study to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell ALL and B-cell lymphoblastic lymphoma. A single arm study design is supported by the absence of effective therapies in this setting, and high unmet medical needs. This study will enroll approximately 67 patients to allow 50 patients treated. After assessment of eligibility, patients qualifying for the study will be enrolled and start lymphodepleting chemotherapy as indicated per protocol, followed by a single dose of CTL019 transduced cells.

The initial 30 patients were treated with the University of Pennsylvania manufacturing process. The remaining patients to be treated on this trail will utilize product manufactured by the Novartis manufacturing process.

The efficacy of CTL019 will be evaluated through the primary endpoint of ORR (ORR = CR + CRi) as determined by Independent Review Committee (IRC) assessment, including CR and CRi. The choice of ORR as the primary endpoint is based on evidence that ORR: 1) Is a standard outcome measurement in ALL and lymphoblastic lymphoma; and 2) the established correlation with long-term outcome ([Cheson et al 2003](#), [Appelbaum et al 2007](#), [NCCN v1 2013](#)).

2.2.1 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation ([Dummer et al 2002](#)), a recent finding that naive T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naive T cells are reduced below a certain threshold ([Goldrath and Bevan 1999](#), [Surh and Sprent 2000](#)). Host lymphodepletion may enhance the effectiveness of adoptively transferred T cells ([Dummer et al 2002](#)). Homeostatic T cell proliferation can lead to activation of certain immune cell subsets ([King et al 2004](#)), providing a clue to improved anti-tumor responses. T cells can undergo up to seven rounds of cell division after being deprived of contact with antigen presenting cells ([Kaech and Ahmed 2001](#), [van Stipdonk et al 2001](#)). Lymphodepletion eliminates regulatory T-cells and other competing elements of the immune system that act as “cytokine sinks”, enhancing the availability of cytokines such as IL-7 and IL-15 ([Klebanoff et al 2005](#)). This hypothesis has been tested clinically in patients with metastatic melanoma refractory to conventional treatments ([Dudley et al 2002](#)). The patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide (60 mg/kg x 2 days) and fludarabine (25 mg/m² x 5 days) prior to adoptive transfer of T cells. Patients with myeloma have been treated with CARs and lymphopenia after lymphodepleting chemotherapy, and observed improved engraftment



(Laport et al 2003, Rapoport et al 2005). In this protocol, it is proposed to infuse CTL019 T cells into patients that are rendered lymphopenic as a result of cytotoxic chemotherapy. Recent data indicates that the increased antitumor efficacy of adoptive transfer following host conditioning is more than simply “making room” because the quantitative recovery of adoptively transferred T cells in mice reveals that *in vivo* proliferation following adoptive transfer is identical in mice with or without previous irradiation (Palmer et al 2004).

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

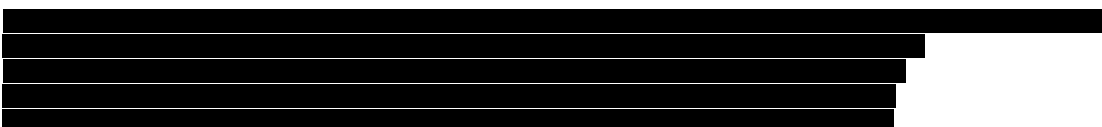
2.3 Rationale for dose and regimen selection

Animal studies support a threshold dose of CTL019 cells and therefore the initial clinical dose selection was within the range of 1×10^7 to 1×10^9 CTL019 transduced cells (Milone et al 2009). Please see IB for further information on preclinical studies. For safety reasons, initial phase I cell dosing was divided among three split infusions (10%, 30% and 60% of the total cell dose). Of the 26 pediatric ALL patients that had a complete remission, seven patients received a single infusion due to the onset of fevers, yet CRs were observed with either 1 to 3 infusions.

In phase I CLL studies, patients have shown responses after a single infusion or multiple infusions. In the phase II CLL trial, the dose has been given as a single infusion of 1 to 5×10^7 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 two 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 >10,000 fold) *in vivo*. Thus, the administered dose may underestimate the number of CTL019 cells *in vivo* following engraftment and expansion and will vary from patient to patient. Additional considerations in this dose selection take into account the manufacturing feasibility of producing adequate numbers of CTL019 transduced cells.

In pediatric ALL patients who were treated in the CHP959 study, patients received one, two or three CTL019 infusions. Tumor responses were seen with each of these dosing schedules. Nineteen patients within the CHP959 study received only a single infusion of CTL019 due to the onset of fever with a cell range of 1.1×10^6 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 CTL019 cells/kg may be associated with a lack of response or CR with an early relapse.

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.

Therefore, the targeted CTL019 cell dose for pediatric ALL patients is 2 to 5×10^6 CTL019 transduced viable T cells per kg body weight with a maximum dose of 2.5×10^8 CTL019 transduced viable T cells (non-weight adjusted).

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparator drugs

Not applicable.

3 Objectives and endpoints

Objectives and related endpoints are described in [Table 3-1](#) below. These objectives will be assessed in the acute lymphoblastic leukemia patients and separately in the lymphoblastic leukemia patients.

If there are no more than 5 lymphoblastic lymphoma patients treated, data for these patients will be summarized primarily via listings.

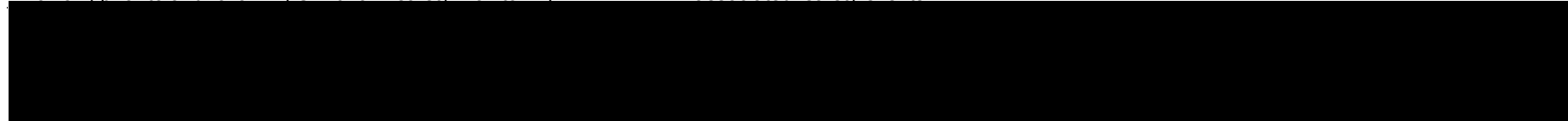


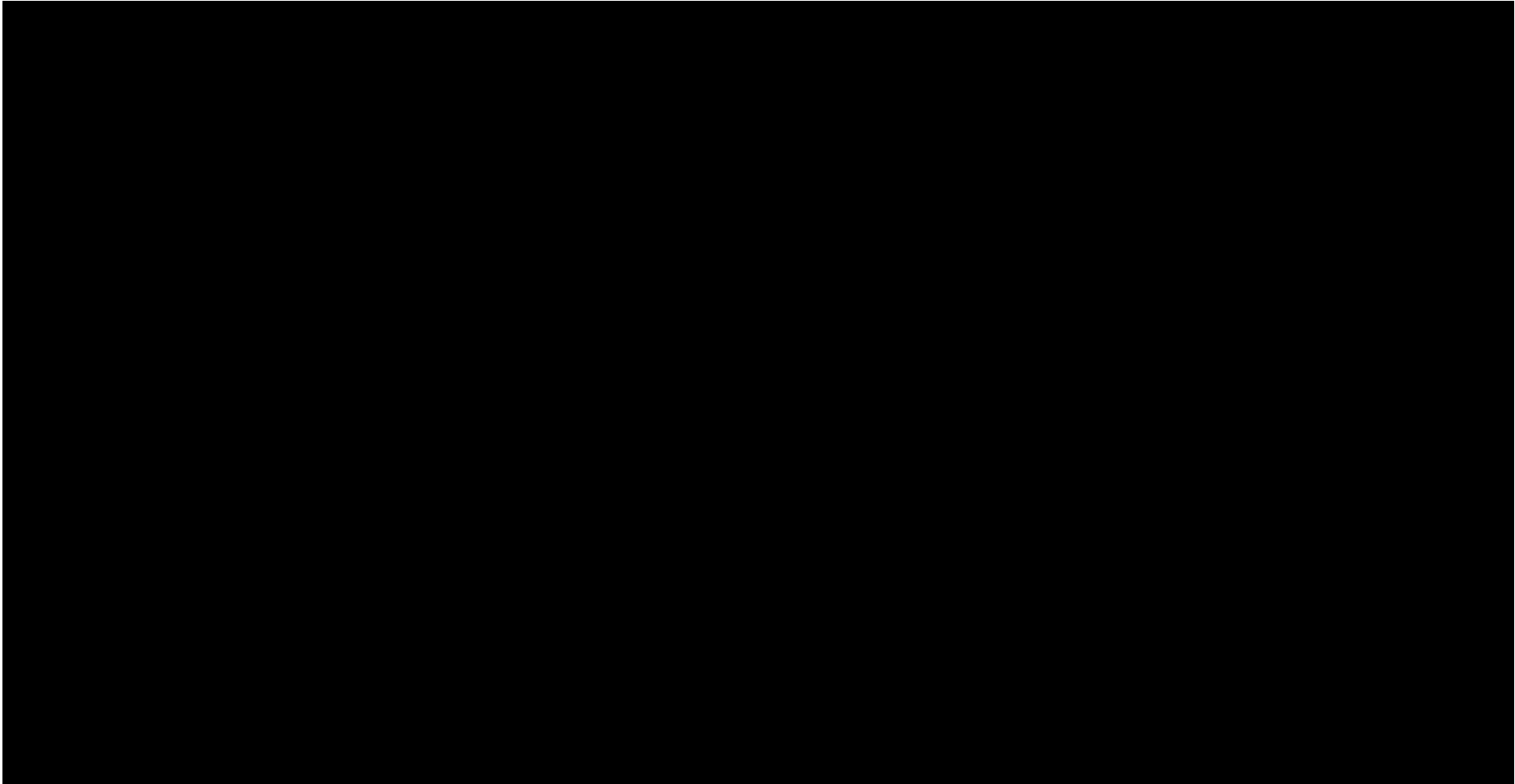
Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
<p>Evaluate the efficacy of CTL019 therapy as measured by overall remission rate (ORR) 6 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment for acute lymphoblastic leukemia patients.. ORR in Lymphoblastic Lymphoma patients will be evaluated separately using local investigator's assessment.</p>	<ul style="list-style-type: none"> ● ORR (= CR + CRi) per IRC assessment in ALL patients; See Appendix 1 for response definition ● ORR (= CR + CRi) per local investigator's assessment in lymphoblastic lymphoma patients; See Appendix 2 for response definition 	Refer to Section 10.4
Key secondary		
Not applicable	Not applicable	
Other secondary		
Evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment	<ul style="list-style-type: none"> ● Percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment 	Refer to Section 10.5.2.1
Evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment	<ul style="list-style-type: none"> ● Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment ● In addition, all patients that proceed to SCT after CTL019 infusion will be described 	Refer to Section 10.5.2.2
Evaluate the duration of remission (DOR)	<ul style="list-style-type: none"> ● DOR, i.e. the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to ALL ● Site of involvement of subsequent relapse will be summarized 	Refer to Section 10.5.2.3
Evaluate the quality of response by assessing the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a minimal residual disease (MRD) negative bone marrow 6 months after CTL019 infusion and at D28 by central analysis	<ul style="list-style-type: none"> ● Percentage of patients with BOR of CR or CRi with MRD negative bone marrow 6 months after CTL019 infusion, among all patients who are infused ● MRD status before treatment, at day 28 +/- 4 days after treatment will also be described 	Refer to Section 10.5.2.4
Evaluate the relapse-free survival (RFS)	<ul style="list-style-type: none"> ● RFS, i.e. the time from achievement of CR or CRi whichever occurs first to relapse or death due to any cause during CR or CRi 	Refer to Section 10.5.2.5
Evaluate the event-free survival (EFS)	<ul style="list-style-type: none"> ● EFS, i.e. the time from date of CTL019 infusion to the earliest of death, relapse or treatment failure 	Refer to Section 10.5.2.6



Objective	Endpoint	Analysis
Evaluate the overall survival (OS)	<ul style="list-style-type: none"> OS, i.e. the time from date of CTL019 infusion to the date of death due to any reason 	Refer to Section 10.5.2.7
Evaluate the response at Day 28 +/- 4 days	<ul style="list-style-type: none"> Proportion of patients attaining CR or CRi at Day 28 +/- 4 days post CTL019 infusion 	Refer to Section 10.5.2.8
Evaluate the impact of baseline tumor burden on response	<ul style="list-style-type: none"> Response as a function of baseline tumor burden (tumor load) (MRD, extramedullary disease, etc) 	Refer to Section 10.5.2.9
Evaluate the safety of CTL019 therapy	<ul style="list-style-type: none"> Type, frequency and severity of adverse events and laboratory abnormalities 	Refer to Section 10.5.3
Characterize the <i>in vivo</i> cellular pharmacokinetic (PK) profile (levels, persistence, trafficking) of CTL019 cells in target tissues (blood, bone marrow, CSF, and other tissues if available)	<ul style="list-style-type: none"> CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available Expression of CTL019 detected by flow cytometry in blood and bone marrow Cmax, Tmax, AUCs and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF if available Maximum extent of expansion of CTL019 in blood (Cmax/Cpost-infusion,hr) Persistence of CTL019 in blood, bone marrow, andCSF (based on Time > Limit of Quantification [LOQ], Time > other threshold CTL019 levels, Mean Residence Time [MRT] last) 	Refer to Section 10.5.4
Describe the prevalence and incidence of immunogenicity to CTL019	<ul style="list-style-type: none"> Prevalence and incidence of immunogenicity and anti-CTL019 assay titers 	Refer to Section 10.5.3.4
Describe the profile of soluble immune factors that may be key to cytokine release syndrome	<ul style="list-style-type: none"> Frequent monitoring of concentrations of soluble immune factors in blood 	Refer to Section 10.5.3.6
Describe the levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 in safety monitoring	<ul style="list-style-type: none"> Lymphocyte subsets of B and T cells and description of associated safety events 	Refer to Section 10.5.3.7





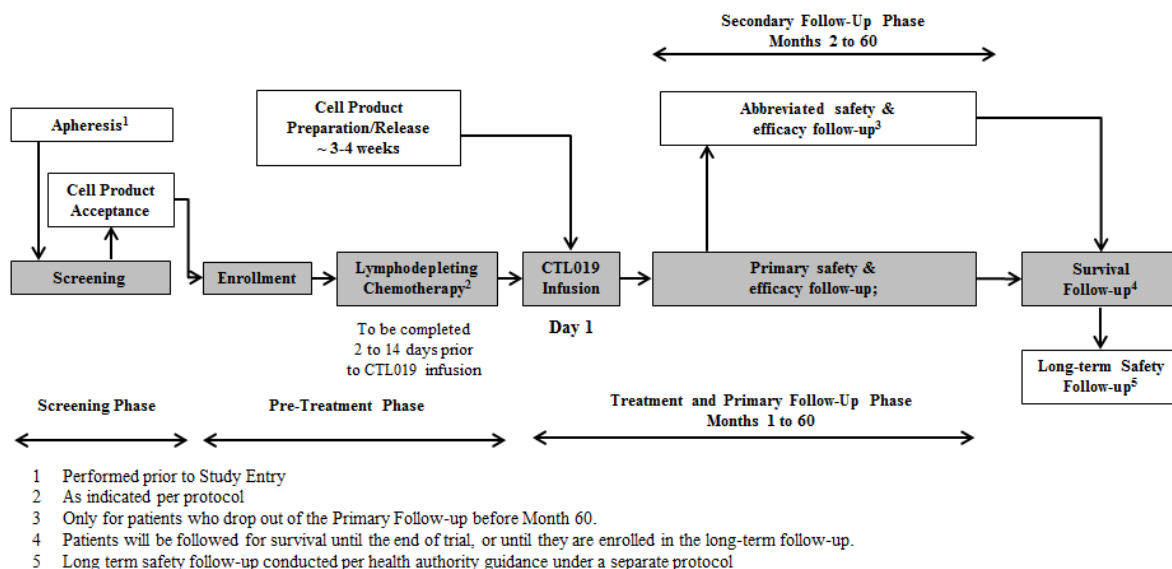
4 Study design

4.1 Description of study design

This is a single arm, multi-center, phase II study to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell ALL and B-cell lymphoblastic lymphoma. The study will have the following sequential phases for all patients: Screening (Section 7.1.1), Pre-Treatment (Cell Product Preparation and Lymphodepleting Chemotherapy; Section 7.1.2), Treatment and Primary Follow-up (Section 7.1.3), Secondary Follow-up (if applicable; Section 7.1.4), and Survival Follow-up (Section 7.1.5). The total duration of the study is 5 years. After CTL019 infusion, efficacy will be assessed monthly for the first 6 months, then quarterly up to 2 years and semi-annually afterwards up to 5 years, or until patient relapse. Efficacy assessments will be based on the Novartis guidelines for response assessment in ALL (Appendix 1), which is based on NCCN version 1.2013 guidelines, Cheson et al (2003) and Appelbaum et al (2007). Safety will be assessed throughout the study. A post-study follow-up (Section 7.1.6) for lentiviral vector safety will continue under a separate destination protocol per the following health authority guidelines: FDA (2006a), FDA (2006b), European Medicines Agency (EMA) (2008) and EMA (2009).

For sites with no prior CTL019 experience, a staggered treatment design will be implemented at each site for the first two patients for logistical and safety purposes. The first patient will be treated and a 14 day follow-up period must be completed before the second patient can be treated. Then a second patient may be treated and a 14 day follow up period completed. After completing this staggered treatment design for the first two patients, subsequent patients may proceed with treatment of patients without staggering.

Figure 4-1 Study design



4.1.1 Apheresis assessment

Cryopreserved apheresis products collected from the patient prior to study entry (historical) may be usable for CTL019 manufacturing if collected at an appropriately certified apheresis center and the product is accepted by the manufacturing facility. If a historical apheresis product is not available, an apheresis procedure will be scheduled for cell procurement prior to study enrollment. It is strongly recommended that apheresis be scheduled prior to any planned chemotherapy or non-physiologic dose of steroid administration as an absolute peripheral blood T-cell count. Subjects with an absolute lymphocyte count (ALC) < 500/ μ L during screening, should have a CD3 count of ≥ 150 / μ L to be eligible for leukapheresis collection.

For guidelines on optimal patient timing of apheresis collection, please refer to the Leukapheresis Key Requirements within the [Leukapheresis, Cryopreservation & Scheduling Manual]. For patients developing grade 2 to 4 acute GVHD or extensive chronic GVHD following the collection of an apheresis product, such an apheresis product cannot be used for CTL019 manufacturing or infusion due to concerns of auto-reactive T cells with an increased risk for inducing or exacerbating GVHD by the manufactured product.

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

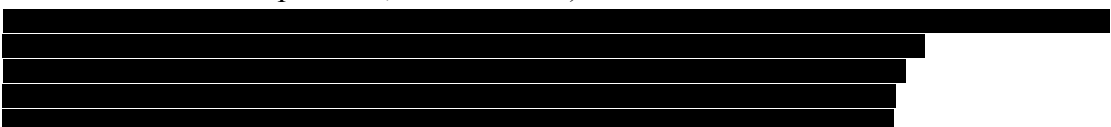


4.2 Definition of end of the study

The end of study is defined as the last patient's last visit (LPLV), which is the last patient's Month 60 evaluation, or the time of premature withdrawal.

Patients who discontinue the "Treatment and Primary Follow-Up Phase" before month 60 will continue to be followed in the secondary follow-up phase in order to collect health authority requested data (e.g. delayed adverse events) up to 5 years after CTL019 infusion. It is anticipated that patients may leave the primary follow-up and move to secondary follow-up due to reasons including: treatment failure, relapse after remission, pursuing SCT while in remission, or withdrawal from the primary follow-up.

In addition, semiannual and annual evaluations will be performed for up to 15 years on all patients under a separate destination protocol as recommended by health authority guidance for patients treated with gene therapies. All patients who either complete the study or prematurely discontinue from the study will be enrolled in this destination protocol at the time of study completion/discontinuation (separate informed consent/assent forms will be provided for this protocol; Section 7.1.6).



Patients may continue to be followed under the current protocol for survival as defined above or until they choose to enroll into the 15 year long term follow-up protocol ([CCTL019A2205B]), whichever occurs first. The survival follow-ups can be conducted in the form of telephone contact.

4.3 Early study termination

The study can be terminated at any time for any reason by Novartis if any of the stopping criteria described in [Section 6.2.4.1.1](#) are met. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. For patients who have received a CTL019 infusion, a long term post-study follow-up for lentiviral vector safety will still continue under a separate destination protocol for 15 years post infusion per health authority guidelines. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the early termination of the trial and any other regulatory committee as applicable.

5 Population

5.1 Patient population

The primary target population consists of pediatric patients with B-cell ALL and lymphoblastic lymphoma who are primary refractory, chemo-refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT. Approximately 67 patients will be enrolled to allow 50 total patients to be treated.

The primary analysis will be comprised of at least 50 acute lymphoblastic leukemia or lymphoblastic lymphoma patients treated.

In order to satisfy European PIP requirement, at least 40 patients <18 years of age will be treated at the time of primary analysis. Therefore, **no more than 10 patients' ≥18 years of age will be treated**. Site will be notified when this cap is reaching.

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

5.2 Inclusion criteria

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

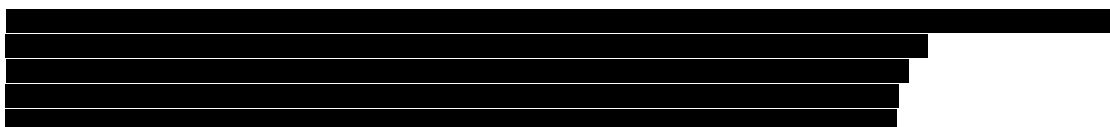
1. [Retired from UPenn protocol version 2.0]
2. For relapsed patients, CD19 tumor expression demonstrated in bone marrow or peripheral blood by flow cytometry within 3 months of study entry
3. Adequate organ function defined as:
 - a. Renal function defined as:
 - Calculated creatinine clearance or radioisotope GFR > 60 mL/min/1.73 m² OR



- A serum creatinine based on age/gender as follows:

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

- b. ALT < 5 times the ULN for age
 - c. Bilirubin < 2.0 mg/dl
 - d. Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation > 91% on room air
 - e. LVSF ≥ 28% confirmed by echocardiogram, or LVEF ≥ 45% confirmed by echocardiogram or MUGA
4. Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening
 5. Life expectancy > 12 weeks
 6. [Retired from UPenn protocol version 2.0]
 7. Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50 at screening
 8. Signed written informed consent and assent forms if applicable must be obtained prior to any study procedures
 9. Once all other eligibility criteria are confirmed, must have an apheresis product of non-mobilized cells received and accepted by the manufacturing site. Note: Apheresis product will not be shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria is received
 10. Relapsed or refractory pediatric B-cell Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma
 - a. 2nd or greater BM relapse OR
 - b. Any BM relapse after allogeneic SCT and must be > 6 months from SCT at the time of CTL019 infusion 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 relapse leukemia OR
 - d. Patients with Ph+ ALL are eligible if they are intolerant to or have failed two lines of 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, including expected outcomes, about the role of SCT with a BMT physician not part of the study team

11. Age 3 at the time of screening to age 21 at the time of initial diagnosis.

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 syndrome: such as patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome. Patients with Down Syndrome will not be excluded.
3. Patients with Burkitt's lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell [sIg positive and kappa or lambda restricted positivity] ALL, with FAB L3 morphology and /or a MYC translocation)
4. Prior malignancy, except carcinoma in situ of the skin or cervix treated with curative intent and with no evidence of active disease
5. Prior treatment with gene therapy product
6. Has had treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
7. [Retired from UPenn protocol version 2.0]
8. [Retired from UPenn protocol version 2.0]
9. Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD)
10. [Retired from UPenn protocol version 2.0]
11. Active CNS involvement by malignancy, defined as CNS-3 per NCCN guidelines. Note: Patients with history of CNS disease that has been effectively treated will be eligible
12. Patient has participated in an investigational research study using an investigational agent within the last 30 days prior to screening
13. Pregnant or nursing (lactating) women. NOTE: female study participants of reproductive potential must have a negative serum or urine pregnancy test performed within 48 hours before infusion
14. [Retired from UPenn protocol version 2.0]
15. Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening
16. HIV positive test within 8 weeks of screening
17. The following medications are excluded:
 - a. **Steroids:** Therapeutic doses of steroids must be stopped > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: < 12 mg/m²/day hydrocortisone or equivalent
 - b. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
 - c. **GVHD therapies:** Any drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion (e.g. calcineurin inhibitors, methotrexate or other chemotherapy



drugs, mycophenolate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-TNF, anti-IL6 or anti-IL6R)

d. **Chemotherapy:**

- The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: hydroxyurea, vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m², cytosine arabinoside < 100 mg/m²/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/m², anthracyclines, cyclophosphamide), excluding the required lymphodepleting chemotherapy drugs
- Pegylated- asparaginase must be stopped >4 weeks prior to CTL019 infusion

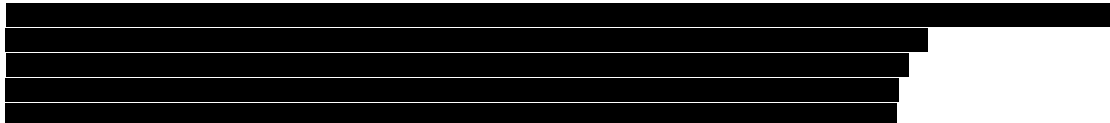
e. **CNS disease prophylaxis:**

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

f. **Anti T-cell Therapy:** Administration of any T cell lytic or toxic agent (e.g. alemtuzumab) prior to CTL019 is strongly discouraged 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 Novartis, consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.

18. Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants, unless they are using highly effective methods of contraception for a period of 1 year after the CTL019 infusion). Women are to continue contraception until CAR cells are no longer present in the blood by PCR. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
- Use of IUDs are excluded due to increased risks of infection and bleeding in this population.
- In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment



Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months (i.e. have had no menses) or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception. Women who are not yet of reproductive potential are to agree to use acceptable forms of contraception when they reach reproductive potential if within 1 year of CTL019 or if CAR cells are present in the blood by PCR. Acceptable documentation includes written or oral documentation communicated by clinician or clinician's staff of one of the following:

- a. Demographics show age <11
- b. Physical examination indicates Tanner Stage 1
- c. Physician report/letter
- d. Operative report or other source documentation in the patient record
- e. Discharge summary
- f. Follicle stimulating hormone measurement elevated into the menopausal range

6 Treatment

6.1 Study treatment

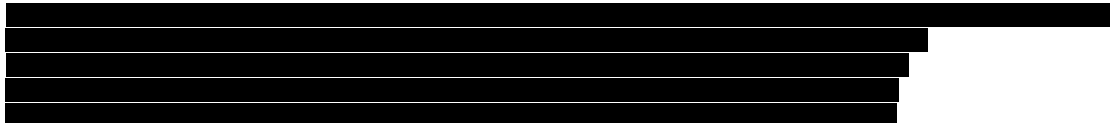
CTL019 is an autologous cellular immunotherapy product that is comprised of CD3+ T cells that have undergone *ex vivo* T cell activation, gene modification, expansion and formulation in infusible cryomedia. The transgene to be expressed via lentiviral vector transduction is a CAR targeted against the CD19 antigen. The CAR contains a murine scFv that targets CD19 linked to a transmembrane region derived from the CD8 receptor, which is linked to an intracellular bipartite signaling chain of TCR- ζ (or CD3- ζ) and 4-1BB intracellular signaling domains. The extracellular scFv with specificity for CD19 is derived from a murine monoclonal antibody. T cells 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. The residual non-integrated vector is washed away during the process. CTL019 cells generally are expanded *ex vivo* for up to 10 days or may be more depending on manufacturing conditions. At the end of the culture, the CTL019 cells are depleted of magnetic beads, washed, concentrated, and cryopreserved. The product must pass all release criteria prior to infusion.

A dose of CTL019 transduced cells for pediatric patients will consist of a single infusion of 2 to 5×10^6 CTL019 transduced cells per kg body weight with a maximum dose of 2.5×10^8 CTL019 cells (non-weight adjusted).

6.1.1 Dosing regimen

6.1.1.1 Lymphodepleting chemotherapy

When given, lymphodepleting chemotherapy should be started before CTL019 infusion so that CTL019 cells will be given 2 to 14 days after completion of the lymphodepleting chemotherapy. The chemotherapy start date will vary based on the selected chemotherapy.



The purpose of this chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CTL019 cells. For lymphodepleting chemotherapy, cyclophosphamide-based regimens are the agents of choice as there is the most experience with the use of these agents in facilitating adoptive immunotherapy. The required lymphodepleting regimen is:

- Fludarabine (30 mg/m² intravenously [i.v.] daily for 4 doses) and cyclophosphamide (500 mg/m² i.v. daily for 2 doses starting with the first dose of fludarabine)

If there was previous Grade 4 hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated resistance to a previous cyclophosphamide-containing regimen, then the following will be used:

- Cytarabine (500 mg/m² i.v. daily for 2 days) and etoposide (150 mg/m² i.v. daily x 3 days starting with the first dose of cytarabine)

If patients have a White Blood Cell (WBC) count \leq 1,000 cells/ μ L within one week prior to CTL019 infusion, lymphodepleting chemotherapy is **NOT** required.

6.1.1.2 CTL019 infusion

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

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

1. **Influenza Testing:** All patients must undergo a rapid influenza diagnostic test (only during the months of October through May) within 10 days prior to the planned CLT019 infusion. If the patient is positive for influenza, oseltamivir phosphate or zanamivir should administered for 10 days as preventative treatment (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their 10 day preventative treatment course prior to receiving CTL019. The test does not need to be repeated prior to CTL019 infusion however if flu-like or respiratory signs and symptoms are present, CTL019 infusion should be delayed until patient is asymptomatic.
2. **Performance Status:** Patient should not experience a significant change in clinical or performance status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with experimental cell infusion.
3. **Laboratory Abnormalities:** Patients experiencing laboratory abnormalities after enrollment, that in the opinion of the treating investigator or PI may impact subject safety or the subjects' ability to receive the CTL019 infusion, may have their infusion delayed until it is determined to be clinically appropriate to proceed with the CTL019 infusion
4. **Leukemia Disease Status:** Prior to CTL019 infusion and following lymphodepleting (LD) chemotherapy patients must not have accelerating disease, as this will put them at unacceptable risk for severe CRS. Patients should not receive CTL019 infusion if they exhibit significant progression of disease during or following LD chemotherapy as evidenced by:
 - Significant and increasing circulating blasts



- Significant increases in organomegaly
 - Clinical evidence of new CNS disease
5. **Chemotherapy Toxicity:** Patients experiencing toxicities from their preceding lymphodepleting chemotherapy will have their infusion schedule delayed until these toxicities have been resolved (to Grade 1 or baseline). The specific toxicities warranting delay of CTL019 cell infusion include:
 - a. **Pulmonary:** Requirement for supplemental oxygen to keep saturation greater than 91% or presence of progressive radiographic abnormalities on chest x-ray
 - b. **Cardiac:** New cardiac arrhythmia not controlled with medical management. Prior to infusion ECG also required (Table 7-1).
 - c. **Hypotension:** requiring vasopressor support
 6. **Infection:** CTL019 infusion must be delayed if there is an uncontrolled active infection, as evidenced by positive blood cultures for bacteria, fungus, or PCR positivity for new viral DNA within 72 hours of CTL019 cell infusion, or clinical or radiographic evidence of active infection. Following the treatment of a recent infection, significant improvement must be established either clinically and/or radiographically, prior to CTL019 infusion
 7. **GVHD Status:** Patients should not be infused if they develop Grade 2-4 acute or extensive chronic GVHD since the time of screening.
 8. **Concomitant Medications:** If patients are taking any of the following medications, their infusion must be delayed until the medications have been stopped according to the following:
 - a. **Steroids:** Therapeutic doses of steroids must be stopped > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: < 12 mg/m²/day hydrocortisone or equivalent
 - b. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
 - c. **GVHD therapies:** Any drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolate, rapamycin, thalidomide, or immunosuppressive antibodies such as rituximab, anti-TNF, anti-IL6 or anti-IL6R)
 - d. **Chemotherapy:**
 - The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: hydroxyurea, vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m², cytosine arabinoside < 100 mg/m²/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/m², anthracyclines, cyclophosphamide), excluding the required lymphodepleting chemotherapy drugs
 - Pegylated- asparaginase must be stopped >4 weeks prior to CTL019 infusion
 - e. **CNS disease prophylaxis:**



1. CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate).
- f. **Anti T-cell Therapy:** Administration of any T cell lytic or toxic agent (e.g. alemtuzumab) prior to CTL019 is strongly discouraged 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 Novartis, consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.
1. **Stem Cell Transplant:** Reconfirm that patient is > 6 months from SCT at the time of CTL019 infusion (if applicable).
9. **Lymphodepleting Chemotherapy Timing:** If there is a delay of 4 or more weeks between completion of lymphodepleting chemotherapy and the scheduled infusion, the WBC > 1000/ μ L, the patient will need to be re-treated with lymphodepleting chemotherapy.
10. **Cardiac Evaluations:** In the event that the time between screening cardiac ECHO/MUGA and CTL019 infusion exceeds 6 weeks, cardiac imaging must be repeated to confirm a LVSF \geq 28% by echocardiogram, or LVEF \geq 45% by echocardiogram or MUGA.
11. **Pregnancy:** Patient must undergo a pregnancy test (urine or serum) within 48 hours prior to infusion (Table 7-1)

Additional safety procedures prior to administration: The risk of tumor lysis syndrome (TLS) is dependent on disease burden. Patients will be closely monitored both before and after lymphodepleting chemotherapy and CTL019 infusions including blood tests for potassium and uric acid. Patients with elevated uric acid or high tumor burden should receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat). Infection prophylaxis should follow local guidelines dictated only by the preceding lymphodepleting chemotherapy. Infection prophylaxis per se for CTL019 is not recommended. **The on-site pharmacy must confirm that two doses of tocilizumab (Section 6.1.3) is on site prior to CTL019 infusion and available for administration in order to manage severe suspected toxicities.**

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

Cell thawing and infusion of CTL019 product:

A study physician MUST evaluate the patient just prior to infusion to ensure the patient meets CTL019 infusion criteria. Trained study staff will administer the CTL019 infusion using precautions for immunosuppressed patients. Protective isolation should follow institutional



standards and policies. Emergency medical equipment should be available during the infusion in case the patient has a significant reaction to the infusion such as anaphylaxis or severe hypotension. A single dose of 2 to 5 x 10⁶ autologous CTL019 transduced viable T cells per kg body weight, with a maximum dose of 2.5 x 10⁸ autologous CTL019 transduced viable T cells will be administered. For patients with manufactured cell numbers falling below the above recommended dose ranges, CTL019 therapy will still be administered if product meets all other manufacturing release criteria.

Depending on the volume of the CTL019 product, it will be given either as an IV infusion through a latex free i.v. tubing WITHOUT a leukocyte filter (approximately 10 – 20 mL per minute adjusted as appropriate for smaller children and smaller volumes) or as an IV push via a syringe (for smaller volumes). It is recommended that the infusion/IV push be completed within 30 minutes of thawing the cryopreserved product. The tubing setup should also contain a Y-arm with an attached supplemental saline bag to be used after the initial infusion is completed. This will allow any remaining product left behind within the bag and tubing to be recovered and infused. Vital signs (temperature, respiration rate, pulse, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion and then approximately every 15 minutes for one hour and repeated at 2 hours. If vital signs are unsatisfactory and unstable, continue to monitor the patient until vital sign stabilization.

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

Following CTL019 infusion: Should emergency treatment be required in the event of life-threatening hypersensitivity or other acute infusion-related reaction, supportive therapy such as oxygen, bronchodilators, epinephrine, antihistamines, and corticosteroids should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Patient or patient's caregiver should monitor the patient's temperature twice daily for the first 14 days post CTL019 infusion. The patient or patient's caregiver should be instructed to call the investigator promptly with any signs of fever for possible hospitalization.

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

6.1.2 Ancillary treatments

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



6.1.3 Rescue medication

Rescue medications are medications given for severe CRS due to CTL019 cells. Please see [Figure 6-1](#). CTL019 administration may require tocilizumab (recommended label dose 8 mg/kg for patients weighing ≥ 30 kg, and 12 mg/kg for patients weighing < 30 kg) or other anti-cytokine therapy for the treatment of suspected CRS toxicities as described below in [Section 6.2.4.2](#). The on-site pharmacy must confirm that two doses of tocilizumab are on site and available for administration **prior to CTL019 infusion**. All rescue medications (except for tocilizumab or other cytokine therapy administration), including steroids given to treat CRS, must be listed on the concomitant medication CRF. Tocilizumab or anti-cytokine therapy administration should be reported on the “Tocilizumab Dose Administration” or “Concomitant Medication” eCRF, respectively.

6.1.4 Guidelines for continuation of treatment

Not applicable.

6.1.5 Treatment duration

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

6.2 Dose escalation guidelines

Not applicable.

6.2.1 Starting dose rationale

Not applicable.

6.2.2 Provisional dose levels

Not applicable.

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

Not applicable.

6.2.3.1 Implementation of Dose Escalation Decisions

Not applicable.

6.2.3.2 Intra-Patient dose escalation

Not applicable.

6.2.3.3 Use the following text for intra-patient dose escalation for combinations

Not applicable.



6.2.4 Definitions of dose limiting toxicities (DLTs) in a Phase II Study

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

6.2.4.1 Toxicity Management, Stopping Rules and Study Termination

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

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

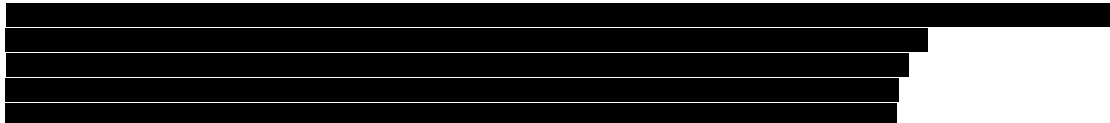
6.2.4.1.1 Criteria for stopping or pausing the study

The study will be paused pending notification of the health authorities and the DMC for investigation and possible protocol amendment if any patient experiences any of the following events within three weeks of the CTL019 cell infusion:

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

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

- Any patient develops uncontrolled T cell proliferation beyond 8 weeks from CTL019 cell product infusion that does not respond to management
- Any patient develops detectable replication competent lentivirus (RCL) during the study
- Novartis or health authorities decides for any reason that patient safety may be compromised by continuing the study
- Novartis decides to discontinue the development of the intervention to be used in this study



6.2.4.2 General toxicity management considerations

Acute Infusion reaction

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

Febrile reaction

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

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

Data from CTL019 treated patients experiencing CRS show marked elevations in IL6 and IFN-g. The symptoms occur in patients with ALL 1-14 days after cell infusion and may include high fevers, rigors, myalgia/arthralgias, nausea/vomiting/anorexia, fatigue, headache, encephalopathy, hypotension, dyspnea, tachypnea and hypoxia. Supportive care and tocilizumab 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 dose of tocilizumab (within 3-5 days) with CRS resolution. One fatal outcome associated with CRS has been observed in an adult ALL patient.

Other anti-cytokine therapies may also be considered if the patient does not respond to tocilizumab. If the patient experiences ongoing CRS despite administration of anti-cytokine directed therapies, anti-T-cell therapies such as cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab may be considered and need to be captured in case report forms.

A detailed treatment algorithm has been established with clear criteria for CRS management and guidance on when to administer tocilizumab and is presented below in [Figure 6-1](#). 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 near to the treating site for the first 21 days.

The management of CRS is based solely upon clinical parameters as described in [Figure 6-1](#) and must be followed by the investigator. [REDACTED]

[REDACTED]

[REDACTED]

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

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

Figure 6-1 CRS Management Algorithm:

Pretreatment

Acetaminophen/paracetamol and diphenhydramine /H1 anti-histamine

Prophylaxis for complications of TLS as appropriate

CTL019 infusion

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

Observation, rule out infection (surveillance cultures)

Antibiotics per local guidelines (febrile neutropenia)

Symptomatic support

Symptom progression: High fevers, hypoxia, mild hypotension

1st Line Management:

Oxygen, fluids, low dose vasopressor support, antipyretics

Monitor/manage complications of TLS

Further symptom progression:

- Hemodynamic instability despite intravenous fluids and moderate to “high dose” vasopressor support OR
- Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow Oxygen (O₂) and/or need for mechanical ventilation OR
- Rapid clinical deterioration

2nd Line Management:

Tocilizumab:

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

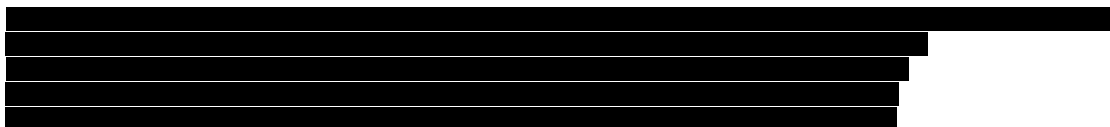
Hemodynamic and respiratory support

Lack of clinical improvement while awaiting tocilizumab response

3rd Line Management:

Steroids (plan rapid taper)

Starting dose 2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day



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

Hemodynamic and respiratory support

Lack of clinical improvement while awaiting response to 3rd line management
4th Line Management:

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

If no response to steroids and 2nd dose of Tocilizumab, consider other anti-cytokine therapies

Hemodynamic and respiratory support

Lack of clinical improvement while awaiting response to 4th line management
5th Line Management:

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

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

Hemodynamic and respiratory support

**Table 6-1 CTL019-Therapy-Associated Grading for Cytokine Release Syndrome:
The Penn Grading Scale for Cytokine Release Syndrome (PGS-CRS)**

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 liver function tests [LFTs]) related to CRS and not attributable to any other condition. Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including Grade 4 LFTs or Grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids* or low dose pressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have Grade 2 CRS.	Life-threatening complications such as hypotension requiring high dose pressors (see Table 6-2) or hypoxia requiring mechanical ventilation.
*Defined as: multiple fluid boluses for blood pressure support			

- Marked elevations in IL-6, interferon gamma and less intensely TNF
- Symptoms occur 1 to 14 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.



Table 6-2 High Dose Vasopressor Use

Definition of “High-Dose” Vasopressors	
Vasopressor	Dose for ≥ 3 hours
Norepinephrine monotherapy	≥ 0.2 mcg/kg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200mcg/min
Epinephrine monotherapy	≥ 0.1 mcg/kg/min
If on vasopressin	High-dose if vaso + Norepinephrine Equivalent (NE) of ≥0.1 mcg/kg/min (using VASST formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 mcg/min (using VASST formula)
VASST Trial Vasopressor Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷ 10] Criteria from Russell et al, NEJM 2008 . Note: Pediatric weight adjustments should be taken into consideration.	

Tumor lysis syndrome

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

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

Laboratory and clinical TLS is defined as follows:

- **Laboratory TLS** is defined as two or more of the following values within three days before or in the days following CTL019 infusion.
 - Uric acid ≥ 8 mg/dL or 25% increase from baseline
 - Potassium ≥ 6 mEq/L or 25% increase from baseline
 - Phosphorus ≥ 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
- **If zero or one of the laboratory values above are abnormal**, continue to manage with allopurinol or a non-allopurinol alternative (e.g. febuxostat) and oral hydration. Consider



IV fluids and rasburicase if uric acid levels remain elevated, and consider in hospital monitoring

- **If Laboratory TLS exists**, manage with i.v. fluids, laboratory blood tests every 6 to 8 hours and inpatient care. Cardiac monitoring should be considered, and rasburicase should be considered if uric acid levels remain elevated
- **Clinical TLS** is defined as the presence of laboratory TLS plus ≥ 1 of these criteria in the absence of other causes.
 - Serum creatinine ≥ 1.5 times the upper limit of the age-adjusted normal range
 - Symptomatic hypocalcemia
 - Cardiac arrhythmia
 - **If Clinical TLS exists**, manage with IV fluids, laboratory blood tests every 6 to 8 hours, cardiac monitoring, rasburicase/allopurinol/febuxostat and inpatient care (consider ICU)

Criteria modified from [Cairo and Bishop \(2004\)](#).

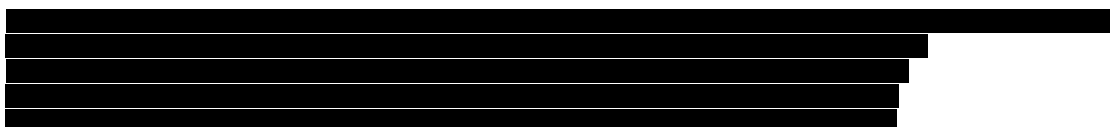
Graft-Versus-Host Disease (GVHD)

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

As part of the exclusion criteria for this protocol regarding GVHD, the grading & staging assessment of acute GVHD will follow the criteria described below in [Table 6-3](#), and the definition of chronic GVHD will follow the criteria described in [Table 6-4](#).

Table 6-3 Staging & Grading of Acute Graft-Versus-Host Disease

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



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

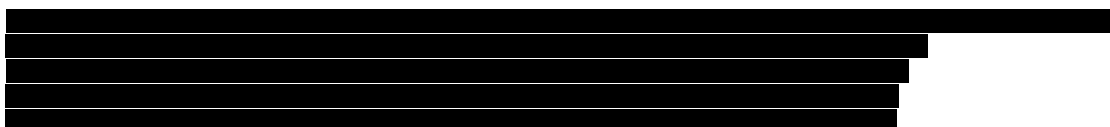
Chronic GVHD is an immune-mediated disorder that may occur following allogeneic SCT. Manifestations include scleroderma, dry eyes, dry mouth, lichenoid oral changes, bronchiolitis obliterans, vanishing bile ducts, or weight loss. It is to be diagnosed specifically rather than diagnosed when acute GVHD-like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

Table 6-4 Definitions of Chronic Graft-Versus-Host Disease

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

Limited Chronic GVHD

- Localized skin involvement and/or liver dysfunction **OR**



- Involvement of only one target organ

Extensive Chronic GVHD

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

B cell depletion

Transient or permanent B cell depletion is a risk with CTL019 therapy, since normal B cells express CD19. This is expected to resolve if and when the CTL019 cells are cleared. Depletion of B cells with resulting hypogammaglobulinemia is expected as a result of CTL019 on target effects in patient with sustained tumor response. CTL019 related hypogammaglobulinemia is typically managed with immunoglobulin replacement therapy dependent upon age specific, disease specific and local institutional guidelines. Immunoglobulin replacement during the study period will be recorded. In general B cell aplasia and hypogammaglobulinemia, of various causes, can be associated with increased rates of infection. Such infections are typically sinopulmonary but other sites and types of infections have also been reported.

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

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

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

6.2.4.3 Potential toxicities

Progressive Multifocal Leukoencephalopathy (PML)

PML is rare but well described with antibody therapies causing B cell aplasia ([Weissert 2010](#)). It is a demyelinating disease of the central nervous system, resulting from infection of oligodendrocytes and astrocytes, mostly with JC virus. PML classically has a subacute clinical presentation with focal neurologic deficits, such as weakness, speech difficulties, unsteady gait and hemiparesis. Ophthalmic symptoms are relatively common, occurring as



homonymous hemianopia which progresses to cortical blindness. Seizure and headache are uncommon. Dementia manifesting as mental deficits in cognition, personality changes, and memory impairment are also common, but it is almost invariably associated with the focal neurologic deficits of PML. By CT or MRI radiographic assessment, lesions are confined to the white matter, most commonly of the occipitoparietal lobe and without mass effect.

In general, patients with known B cell aplasia are at increased risk for PML. Therefore patients in the study will be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated. Please see current guidelines for work up and treatment for PML (NINDS Progressive Multifocal Lekoencephalopathy 2015).

Hepatitis B reactivation

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

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

Immunogenicity

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



experienced an anaphylactic reaction after multiple, repeated injections of a CAR with a murine based scFv ([Maus et al 2013](#)). Impaired function of CEA- targeting autologous T cells has been observed *in vitro* following exposure to receptor specific IgG obtained from treated patients. ([Parkhurst et al 2011](#)).

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

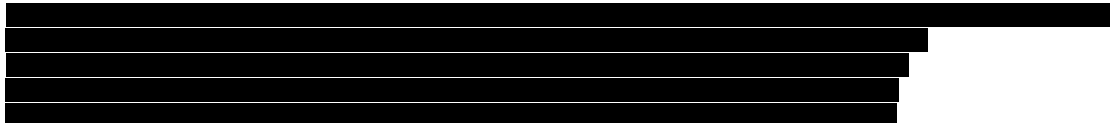
Replication-competent lentivirus (RCL) testing

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

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

Clonality and insertional oncogenesis

Four of nine treated patients in a gene therapy trial for X-linked Severe Combined Immunodeficiency (SCID) developed T cell leukemia 31-68 months post-treatment. The T cell leukemias were attributable to clonal expansion conferred by gammaretroviral vector integration sites in the CD34+ bone marrow stem cell modification ([Hacein-Bey-Abina et al 2008](#)). This represents the most severe adverse event caused by vector integration. However, there is also evidence for retroviral vector integration site dominance in a gene therapy trial of β -thalassaemia without malignancy ([Cavazzana-Calvo et al 2010](#)). The lentiviral vector used for CTL019 manufacturing is part of a vector class that may have a lower risk for integration in or near oncogenic regions than onco-retroviral vectors ([Montini E et al 2009](#)). As of March 2014, none of the patients treated with CTL019 have developed a new malignancy, T cell or otherwise, related to lentiviral vector integration. Subjects will be monitored for evidence of unexpected CTL019 expansion by CTL019 transgene quantitation by qPCR and clinical



monitoring for malignancy by complete blood count (CBC) as part of the study design. If an unexpected pattern of CTL019 expansion is observed (i.e. CTL019 expansion in the absence of CD19+ target), subjects will be closely monitored clinically for new malignancies, particularly T cell, and further studies, including insertion site analysis, will be considered to investigate the molecular basis of the expansion. Investigators should consult Novartis if an unexpected pattern of CTL019 expansion and/or a new malignancy arises. Subjects will be similarly monitored for clonality and insertional oncogenesis when enrolled on the long term follow up protocol.

Uncontrolled T cell proliferation

CTL019 transduced cells could theoretically proliferate without the control of normal homeostatic mechanisms. In pre-clinical studies (Milone et al 2009) and clinical experience to date (Porter et al 2011, Grupp et al 2013), CTL019 transduced cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen. In the context of CTL019 therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be beneficial or harmful depending on the extent of proliferation.

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

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

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

6.2.6 Concomitant Therapy

Clinically significant prescription and nonprescription medication, excluding vitamins, and herbal and nutritional supplements, taken by the patient during the 30 days prior to screening will be recorded. At every visit following the screening visit up to the month 60 visit, concomitant medications will be recorded in the medical record and on the appropriate CRF. During selected trial phases, concomitant medication collection will be modified as outlined in the Modified Data Reporting document and CRF Completion Guidelines (CCGs) (Table 6-5 and Appendix 4). Modified collection of concomitant medications during these trial phases are designed to capture CTL019-related toxicity, severity, interventions and



response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented.

Table 6-5 Concomitant Medication Reporting by Trial Phase

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

See [Appendix 4](#) for further details.

The following guidelines must be adhered to during the study:

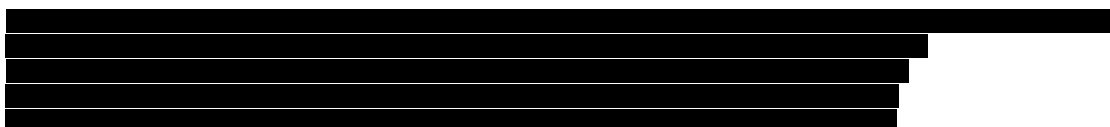
- Granulocyte macrophage-colony stimulating factor (GM-CSF) should be avoided due to the potential to worsen CRS symptoms.
- Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of CTL019 infusion and until CRS is resolved. Long acting G-CSF should not be given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

6.2.7 Prohibited concomitant therapy

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

Specifically, the following medications are excluded:

- 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/m²/day hydrocortisone or equivalent
- Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
- GVHD therapies:** Any drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolate, rapamycin, thalidomide, or immunosuppressive antibodies such as rituximab, anti-TNF, anti-IL6 or anti-IL6R)
- Chemotherapy:**



- The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: hydroxyurea, vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m², cytosine arabinoside < 100 mg/m²/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/m², anthracyclines, cyclophosphamide), 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. Anti T-cell Therapy:** Administration of any T cell lytic or toxic agent (e.g. alemtuzumab) prior to CTL019 is strongly discouraged 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 Novartis, consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.

6.3 Patient numbering, treatment assignment or randomization

6.3.1 Patient numbering

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

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

6.3.2 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.

6.3.3 Treatment blinding

This is an open-label study.



6.4 Study drug preparation and dispensation

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

After logging the CTL019 cells, they will be stored safely and properly ([Section 6.4.2](#)). 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 will 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 returned to the manufacturing facility. This issue should be documented properly and the manufacturing facility notified on handling of compromised product. For further preparation and administration, see [Section 6.1.1.2](#) and the [Investigational Product Handling Manual] (e.g. option of syringe-based administration for pediatric patients with small product volumes).

6.4.1 Study drug packaging and labeling

Each infusion bag will typically contain 10 – 50 mL of cells containing a cell dose of 2 to 10 x 10⁶ CTL019 transduced viable T cells per kg body weight with a maximum dose of 2.5 x 10⁸ CTL019 transduced viable T cells (non-weight adjusted). 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 (see Manual of Procedures). The study number and the wording "FOR AUTOLOGOUS USE ONLY" will be included in the label. In addition the label will have at least two unique identifiers such as the patient's alphanumeric identifier and birth date according to applicable regulations. Additional label elements required by local regulatory guidelines will also be included. Prior to the infusion, two individuals will verify all of this information and confirm identity according to local institutional guidelines, to ensure that the information is correctly matched to the patient, and that the patient receives only their autologous product.

6.4.2 Drug supply and storage

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



6.4.3 Study drug compliance and accountability

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

6.4.3.1 Study drug compliance

As a single administration study, compliance will be assessed by the investigator and/or study personnel and captured in the Drug Accountability Form.

6.4.3.2 Study drug accountability

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

The investigator will dispose used and unused CTL019 cell product, packaging, and product labels. A copy of the completed drug accountability log will then be collected by the study monitor. Please refer to [\[Investigational Product Handling Manual\]](#) for specific details on product destruction.

6.4.3.3 Handling of other study treatment

Not applicable.

6.4.4 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 be disposed of according to local institutional standard operating procedures. Additional guidance is provided in the Investigational Product Handling Manual.

In the event that CTL019 study drug manufactured by Novartis or University of Pennsylvania was not shipped to the site for infusion, it will be managed per manufacturing facility process. The CTL019 product will either be utilized for research purposes or it will be destroyed.

Reconciliation of CTL019 cell product shipped, administered, and remaining, is performed by Novartis (or designee). 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. 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 (Screening to Month 12) and Table 7-2 (Month 15 to Month 60) list all of the assessments through the end of the Treatment and Primary Follow-up phase (Section 7.1.3).

For patients who discontinue early from the Treatment and Primary Follow-Up Phase prior to Month 60, the patient will enter a Secondary Follow-Up Phase to collect health authority requested data (e.g. delayed adverse events, etc.). The first visit in the Secondary Follow-Up Phase is determined according to the time since CTL019 infusion when the patient discontinued from the Treatment and Primary Follow-Up Phase. For example, if the patient discontinued from the Treatment and Primary Follow-Up phase at Month 10, the first visit in the Secondary Follow-Up Phase will be Month 12. Table 7-3 lists all of the assessments through the end of the Secondary Follow-up phase (Section 7.1.4). It is anticipated that patients may leave the primary follow-up and move to secondary follow-up due to reasons including: treatment failure, relapse after remission, pursuing SCT while in remission, or withdrawal from the primary follow-up (See Figure 7-1 below).

In each table, required assessments are indicated with an “X, and the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. No CRF will be used as a source document.

Figure 7-1 Potential Patient flow scenarios

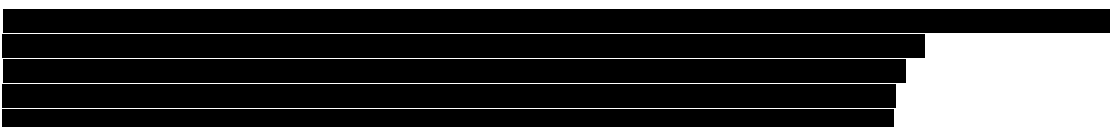
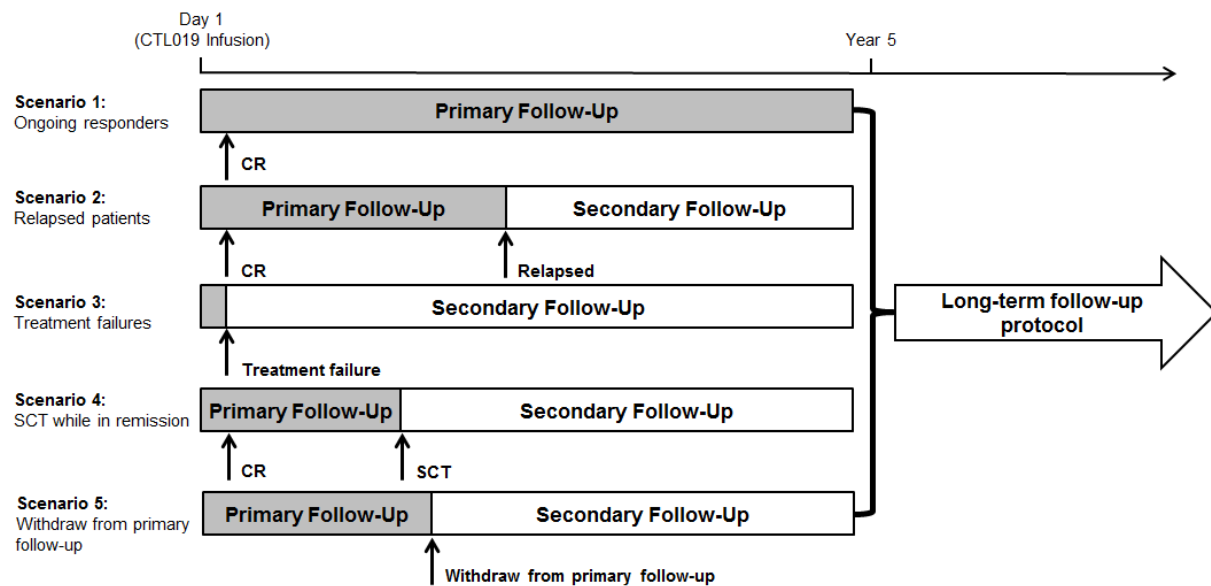


Table 7-1 Visit evaluation schedule

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up																
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion	Infusion	Post Infusion															
Visit Name																							
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	
Obtain Informed Consent	D	7.1.1	X																				
Historical Apheresis	D	4.1.1	X																				
IWRS/IRT	S	7.1.1.1	X	X			X		X	X	X	X		X	X		X			X	X	X	
Patient history																							
Demography	D	7.1.1	X																				
Inclusion/exclusion criteria	D	5.2 5.3	X																				
Medical History (including GVHD assessment)	D	7.1.1 6.2.4.2	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diagnosis and extent of cancer	D	7.1.1	X																				
Cytogenetics / FISH/ [REDACTED]	D	7.1.1	X																				
Donor chimerism	D	7.2.2.5	X																				
Prior antineoplastic therapy	D	7.1.1	X																				

[REDACTED]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up																
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion	Infusion	Post Infusion															
Visit Name																							
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	
Donor chimerism (prior allogeneic SCT patients only)	D	7.2.2.5	X																				
Prior/concomitant medications	D	6.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antineoplastic therapies after CTL019 infusion or study discontinuation	D	7.1.1						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	S	7.2.2.1	X			X		X	X	X		X		X	X	X	X	X	X	X	X	X	X
Performance status	D	7.2.2.4	X			X		X		X		X		X	X	X	X	X	X	X	X	X	X
Height	D	7.2.2.3	X																	X		X	
Tanner staging	D	7.1.1	X																	X		X	
Weight	D	7.2.2.3	X			X									X		X			X	X	X	
Vital signs	D	7.2.2.2	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry	D	7.2.2.2	X				X																
Intervention																							
Lymphodepleting Chemotherapy	D	6.1.1.1			X																		
Other chemotherapy while on study	D	6.2.6	As clinically indicated																				



Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up															
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion	Infusion	Post Infusion														
Visit Name																						
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d
CTL019 infusion prerequisite assessment	S	6.1.1.2					X															
CTL019 transduced cell infusion	D	6.1.1.2					X															
Laboratory assessments																						
Hematology	D	7.2.2.5	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab tests of special interest (██████████, LDH, fibrinogen)	D	7.2.2.5	X		X		X	X	X	X	X	X	X	X	X							
Serum pregnancy test	D	7.2.2.5	X																			
Urine pregnancy test	D	7.2.2.5				X																
HIV test	D	7.2.2.5	X																			
Hepatitis B and C	D	7.2.2.5	X																			
Coagulation factors (PT, aPTT, INR, fibrinogen, D-dimer)	D	7.2.2.5	X				X			X		X			X							



Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up																
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion	Infusion	Post Infusion															
Visit Name																							
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	
Serum immunoglobulin levels (IgG,IgA, IgM)	D	7.2.2.5	X									X			X		X			X	X	X	
MUGA/ECHO	D	7.2.2.6.2	X																				
Electrocardiogram (ECG)	D	7.2.2.6.1	X				X																
Urinalysis	D	7.2.2.5	X																				
Pulse oximetry	D	7.2.2.1	X				X																
Disease Assessments																							
Bone marrow biopsy and aspirate morphology	D	7.2.1	X												X	If patient is not in CR/CRi at D28, then required at time of disease remission at all other sites. For patients in CR/CRi, Month 3 and 6 recommended but not required							



Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up																
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion	Infusion	Post Infusion															
Visit Name																							
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	
Tumor cell assessment by flow cytometry of peripheral blood (includes normal B cell, count and, CD19 status)	D	7.2.1	X							X		X		X	X		X			X	X	X	
Lymph node or other involved tissue biopsy or aspirate	D	7.2.1			As clinically indicated																		
CSF assessment / lumbar puncture	D	7.2.1	X												X	If patient is not in CR/CRi at D28, then required at time of disease remission at all other sites. Otherwise, as clinically indicated by the presence of neurologic symptoms.							
CNS Brain Imaging (MRI / CT)	D	7.2.1		As clinically indicated																			
Mediastinal disease assessment (chest CT scan or MRI) only for lymphoblastic lymphoma patients	D	7.2.1	X												X	If patient is not in CR/CRi at D28, then required at the first time clinical evidence of remission is seen by blood and PE. Otherwise, as clinically indicated.							



Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up																
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion	Infusion	Post Infusion															
Visit Name																							
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	
Extramedullary Disease assessment (physical exam and CNS symptom assessment)	D	7.2.1	X												X	X	X	X	X	X	X	X	X
Safety																							
Adverse events	D	8.1 8.2	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancies and menstrual status	D	7.2.2														X	X	X	X	X	X	X	X
Immunogenicity (serum)	D	7.2.3		X								X			X		X			X			X
Immunogenicity (peripheral blood)	D	7.2.3		X								X			X		X			X			X
RCL by VSV-G Q-PCR (peripheral blood)	D	6.2.4.3		X													X			X			X



Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Infusion	Treatment and Primary Follow-up														
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion		Post Infusion														
Visit Name																						
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d

[Redacted text block]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Infusion	Treatment and Primary Follow-up														
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion		Post Infusion														
Visit Name																						
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d

[Redacted text block]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Infusion	Treatment and Primary Follow-up														
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion		Post Infusion														
Visit Name																						
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d
Survival follow-up	D	7.1.7						For all patients who prematurely discontinue from primary follow-up (regardless of remission status), follow-up for survival every 3 months until end of study or enrolling into the 15 year long term follow-up, whichever comes first														

[Redacted text block]

Phase	Category	Protocol Reference Section	Screening	Pre-Treatment			Treatment and Primary Follow-up															
				Enrollment/Pre-chemotherapy evaluation	Lymphodepleting Chemotherapy	Pre infusion	Infusion	Post Infusion														
Visit Name																						
Study day			W-8 to W-4	W-8to D-8	W-2 to W-1	D-1 +1d	D1	D2	D4 ±1d	D7 ±1d	D11 ±1d	D14 ±3d	D17±3d	D21 ±3d	D28 ±4d	M2 ±14d	M3 ±14d	M4 ±14d	M5 ±14d	M6 ±14d	M9 ±14d	M12 ±14d
End of Phase Disposition	D	N/A	X			X																

Table 7-2 Visit Evaluation Schedule: Treatment and Primary follow-up continued (Month 15 through Month 60)

Phase	Category	Protocol Reference Section	Treatment and Primary Follow-up										End of treatment & primary follow-up	Survival follow-up
			Post infusion											
Visit Name			M15 ±14d	M18 ±14d	M21 ±14d	M24 ±14d	M30 ±14d	M36 ±14d	M42 ±14d	M48 ±14d	M54 ±14d	M60 ±14d	q3m ±14d	
Prior/concomitant medications	D	6.2.6	X	X	X	X	X	X	X	X	X	X		
Physical examinations (PE)	S	7.2.1.1	X	X	X	X	X	X	X	X	X	X		
Performance status assessment	D	7.2.2.3	X	X	X	X	X	X	X	X	X	X		
Height	D	7.2.2.2		X		X	X	X	X	X	X	X		
Tanner Staging	D	7.1.1		X		X	X	X	X	X	X	X		
Weight	D	7.2.2.2		X		X	X	X	X	X	X	X		
Vital signs	D	7.2.2.1	X	X	X	X	X	X	X	X	X	X		
Hematology	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X		



Phase	Category	Protocol Reference Section	Treatment and Primary Follow-up											
			Post infusion										End of treatment & primary follow-up	Survival follow-up
			M15 ±14d	M18 ±14d	M21 ±14d	M24 ±14d	M30 ±14d	M36 ±14d	M42 ±14d	M48 ±14d	M54 ±14d	M60 ±14d		
Visit Name	Study Day													
	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X		
	D	6.2.6	X	X	X	X	X	X	X	X	X	X		
	D	7.2.1	As clinically indicated											
	D	7.2.1		X		X		X		X		X		
	D	7.2.1	As clinically indicated											
	D	7.2.1	As clinically indicated											
	D	7.2.1	As clinically indicated											
	D	7.2.1	X	X	X	X	X	X	X	X	X	X		
Safety														
	D	8.1	X	X	X	X	X	X	X	X	X	X		
	D	7.2.2	X	X	X	X	X	X	X	X	X	X		
	D	7.2.2.4 10.5.3.4				X		X						
	D	7.2.2.4 10.5.3.4				X		X						
	D	6.2.4.3				X		X		X		X		

[REDACTED]

Phase	Category	Protocol Reference Section	Treatment and Primary Follow-up											
Visit Name			Post infusion										End of treatment & primary follow-up	Survival follow-up
Study Day			M15 ±14d	M18 ±14d	M21 ±14d	M24 ±14d	M30 ±14d	M36 ±14d	M42 ±14d	M48 ±14d	M54 ±14d	M60 ±14d	q3m ±14d	
Survival Follow-up	D	7.1.5	For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, whichever comes first. If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact.									X		
End of phase disposition	D	N/A										X		

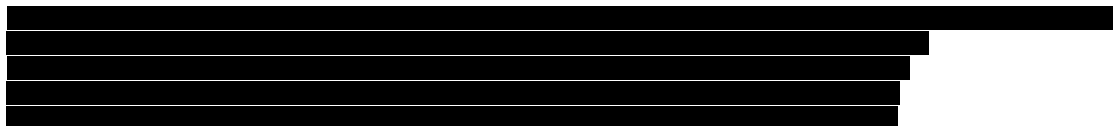


Table 7-3 Visit Evaluation Schedule: Secondary Follow-up

Phase	Category	Protocol Reference Section	Secondary Follow-up														End of Secondary Follow-up	Survival Follow-up
			Post Infusion															
			M2 ±14d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	M15 ±14d	M18 ±14d	M21 ±14d	M24 ±14d	M30 ±14d	M36 ±14d	M42 ±14d	M48 ±14d	M54 ±14d		
Patient History																		
Concomitant medications (selected)	D	6.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Antineoplastic therapies after CTL019 infusion or study discontinuation	D	6.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	D	7.2.2.2			X		X		X		X	X	X	X	X	X	X	
Weight	D	7.2.2.2		X	X	X	X		X		X	X	X	X	X	X	X	
Tanner Staging	D	7.2.2			X		X		X		X	X	X	X	X	X	X	
Vital signs	D	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory assessments																		
Hematology	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy assessments																		
Relapse information (only when patient is in remission)	D	7.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	



Phase	Category	Protocol Reference Section	Secondary Follow-up														End of Secondary Follow-up	Survival Follow-up
			Post Infusion															
Visit Name			M2 ±14d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	M15 ±14d	M18 ±14d	M21 ±14d	M24 ±14d	M30 ±14d	M36 ±14d	M42 ±14d	M48 ±14d	M54 ±14d	M60 ±14d	q3m ±14d
Study Day																		
Safety assessments																		
Protocol defined adverse events, including new malignancies	D	8.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancies and menstrual status	D	7.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination (PE)	S	7.2.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status	D	7.2.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum (immunogenicity, cytokines)	D	7.2.4		X	X		X											
CTL019 transgene persistence (peripheral blood)	D	7.2.3		X	X	X	X		X		X	X	X	X	X	X	X	
Flow Cytometry of peripheral blood (B cell, T cell levels – local assessment)	D	7.2.1		X	X	X	X				X		X		X		X	
DNA RCL by VSV-G q-PCR (peripheral blood)	D	6.2.4.3		X	X		X				X		X		X		X	
Survival follow-up	D	7.1.5	For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, whichever comes first. If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact.														X	



Phase	Category	Protocol Reference Section	Secondary Follow-up													End of Secondary Follow-up	Survival Follow-up
Visit Name			Post Infusion														
Study Day			M2 ±14d	M3 ±14d	M6 ±14d	M9 ±14d	M12 ±14d	M15 ±14d	M18 ±14d	M21 ±14d	M24 ±14d	M30 ±14d	M36 ±14d	M42 ±14d	M48 ±14d	M54 ±14d	M60 ±14d
End of phase disposition	D	N/A														X	



7.1.1 Screening Phase

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

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

Patients should not be enrolled if they are unable to be followed up long-term i.e. 5 years on treatment protocol and 10 additional years follow up as required by the health authorities for cell and gene therapy products.

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

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

- a. Demography
- b. Medical history (including diagnosis and extent of cancer) and prior/concomitant medications and antineoplastic therapies
- c. Physical Examination (PE) including height, weight, GVHD assessment, Tanner staging and vital signs, extramedullary disease assessment and CNS symptom assessment
- d. Performance status (Karnofsky [age \geq 16 years] or Lansky [age < 16 years]) at the time of screening
- e. Standard ALL cytogenetics, FISH, [REDACTED] 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), only if previously received allogeneic SCT)
- g. Complete Blood Count, Differential
- h. Chemistry Panel
- i. Labs of Special Interest ([REDACTED] LDH, and fibrinogen)
- j. Coagulation panel
- k. Urinalysis
- l. Serum pregnancy test (if female of childbearing potential)HIV testing (test within 8 weeks of screening) - If an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines.
- m. Hepatitis B and Hepatitis C test (test within 8 weeks of screening. See Appendix 3 for interpretation of Hepatitis B results)
- n. Serum immunoglobulin levels (IgG, IgA, IgM)
- o. MUGA and/or ECHO (performed within 6 weeks of infusion) for LVSF/LVEF
- p. ECG

[REDACTED]

- q. Pulse oximetry
- r. [REDACTED]
- s. Peripheral blood collection for flow cytometry (B-cell and T-cell numbers, tumor cell numbers, and CD19 assessment)
- t. Lymph node or tissue aspirate or biopsy (if clinically indicated)
- u. [REDACTED]
- v. CNS Brain Imaging (MRI/CT) (if clinically indicated)
- w. Adverse events
- x. Mediastinal disease assessment (chest CT scan or MRI); only with history of mediastinal disease i.e. in patients with r/r lymphoblastic lymphoma

7.1.1.1 Eligibility Screening & Enrollment

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

Once clinical eligibility has been confirmed, only then can the patient's apheresis product be shipped to the manufacturing facility. The manufacturing facility will then evaluate the patient's apheresis product for acceptance and notify the site. Enrollment is defined as the point at which a patient meets all clinical inclusion/exclusion criteria and the patient's apheresis product is received and accepted by the manufacturing facility. The patient is then enrolled using the same Patient No. assigned at screening by the site investigator 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, IRT will be contacted initially after informed consent/assent is obtained and again after eligibility is confirmed.

7.1.1.2 Information to be collected on patient not enrolled

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

[REDACTED]

7.1.2 Pre-Treatment Phase

For details of assessments, refer to [Table 7-1](#).

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

Before the scheduled lymphodepleting chemotherapy regimen is to begin, the patient will undergo blood collection for safety and [REDACTED] humoral & cellular immunogenicity and RCL by VSV-G qPCR. These lab draws are preferably drawn at enrollment, however if not obtained collection can be done any time prior to lymphodepleting chemotherapy. In addition, adverse events and prior/concomitant medications will be reviewed. Samples from the apheresis material as well as the CTL019 product will be collected at the manufacturing site for correlative studies.

Lymphodepleting chemotherapy visit (D-14 to D-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 apheresis, an additional chemotherapy cycle is planned. Patients referred with stable disease on no recent therapy will be eligible as well. The use of additional chemotherapy prior to the recommended pre-infusion chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden.

When given, lymphodepleting chemotherapy should be started before CTL019 infusion so that 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/m² i.v. daily for 4 doses) and cyclophosphamide (500 mg/m² i.v. daily for 2 doses starting with the first dose of fludarabine) is the regimen of choice, as there is the most experience with the use of this regimen in facilitating adoptive immunotherapy. Refer to [Section 2.2.1](#) for additional information regarding lymphodepleting chemotherapy.

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

Patients will also undergo blood tests including chemistry, lab tests of special interest ([REDACTED] fibrinogen, and LDH) , and a CBC with differential. Adverse events and prior/concomitant medications will be reviewed.

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

On the day prior or day of the scheduled CTL019 infusion, patients will undergo a physical exam (including weight and vital signs), and a performance status assessment (Karnofsky (age ≥ 16 years) or Lansky (age < 16 years)). In addition, a urine or serum pregnancy test will be performed on female patients of childbearing potential confirming a negative pregnancy result. In addition, adverse events and prior/concomitant medications will be reviewed.

[REDACTED]

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

7.1.3 Treatment and Primary Follow-Up Phase

For details of assessments, refer to [Table 7-1](#).

Infusion visit (D1)

CTL019 infusion will begin 2 to 14 days after completion of lymphodepleting chemotherapy.

The day of (but prior to) the CTL019 infusion, patients will undergo blood tests including chemistry, labs of special interest ([REDACTED] LDH, and fibrinogen), a CBC with differential and coagulation panel, and serum cytokine. Final CTL019 infusion pre-requisites (including an ECG) will be checked prior to infusion (per [Section 6.1.1.2](#)).

CTL019 transduced T cells will be given as a single dose of 2 to 5 x 10⁶ CTL019 transduced viable T cells per kg body with a maximum dose of 2.5 x 10⁸ CTL019 cells (non-weight adjusted). Vital signs will be monitored before and following CTL019 infusion (per [Section 6.1.1.2](#)). A blood sample will be collected post-infusion for CTL019 PK assessment. In addition, adverse events and prior/concomitant medications will be reviewed.

Details on the administration of the CTL019 infusion are found in [Section 6.1.1.2](#).

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

At the intervals following infusion listed above, patients will undergo one or more of the following: physical exam, blood tests including chemistry, labs of special interest ([REDACTED] LDH, and fibrinogen), hematology, coagulation, serum immunoglobulin, humoral & cellular immunogenicity, CTL019 PK, [REDACTED], flow cytometry (B and T cells, tumor cells and CD19 assessment), a physical exam (with vital signs) and performance status assessment. In addition, adverse events and prior/concomitant medications will be reviewed. On Day 2, only vital signs, physical examination, performance status, hematology, and chemistry (inclusive of LFTs and creatinine) will be performed.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Post-infusion visit (D28 ±4d)

Patients will undergo blood collection for hematology, chemistry, labs of special interest ([REDACTED] LDH, and fibrinogen), coagulation, serum immunoglobulins, [REDACTED], flow cytometry (B and T cells, tumor cells, and CD19 assessment) humoral and cellular immunogenicity, [REDACTED]. Patients will have a lumbar puncture for CSF cytologic assessments and CTL019 PK. Patients are required to have a bone marrow biopsy and aspirate for morphology, flow cytometry, MRD, CTL019 PK, [REDACTED]. In addition, patients will undergo a physical exam (including vital signs, weight, and extramedullary disease assessment), CNS symptom assessments and a performance status assessment. Tumor response assessments will be conducted (see Appendix 1 for response guidelines). A lymph node or tissue aspirate or biopsy may be done if clinically indicated. Adverse events and prior/concomitant medications will be reviewed.

For details of assessments, refer to [Table 7-1](#).

Post-infusion visits (Monthly from M2 through M6 ±14d)

At the intervals following infusion listed above, patients will undergo one or more of the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B and T cells, tumor cells, and CD19 assessment), cytokines, humoral & cellular immunogenicity and [REDACTED], and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including vital signs, height, weight, Tanner staging (month 6 only), and extramedullary disease assessment), CNS symptom assessment, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed.

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

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

For details of assessments at each visit, refer to [Table 7-1](#).

Post-infusion visit (M9 ±14d)

Patients will undergo one or more of the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B and T cells, tumor cells, and CD19 assessment), and CTL019 PK. In addition, patients will undergo a physical exam (including vital signs and extramedullary disease assessment), CNS symptom assessment and a

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

performance status assessment. Adverse events and prior/concomitant medications will be reviewed.

For details of assessments, refer to [Table 7-1](#).

Post-infusion visit (M12 ±14d)

Patients will undergo the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B and T cells, tumor cells, and CD19 assessment), cytokines, humoral and cellular immunogenicity, [REDACTED] and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including height, weight, GVHD assessment, Tanner staging, vital signs, and extramedullary disease assessment), CNS symptom assessment, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed.

For details of assessments, refer to [Table 7-1](#).

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

If $\geq 1\%$ of the WBC in peripheral blood are positive for CD19 CAR vector sequences by qPCR at > 12 months from CD19 CART infusion, then the patient will be asked to return for a confirmatory blood test prior to the next visit. If $\geq 1\%$ of the WBC is positive upon the receipt of the confirmatory qPCR result, then the genomic vector integration sites will be determined. Identified vector integration sites will be evaluated using bioinformatic approaches to determine the frequency of integration events in regions with known relationships to human cancers (i.e. near oncogenes). If integration site analysis reveals mono- or oligo-clonality pattern and/or integration at or near an oncogenic locus, a monitoring plan, including follow-up molecular analyses, will be developed in collaboration between the Investigator, Novartis and Health Authorities that is specific for the health care risks that are anticipated given the nature of the integration site and vector target cell type.

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

Patients will undergo the following: blood collection for hematology, chemistry and CTL019 PK. Blood will be collected for flow cytometry (B and T cells, tumor cells) at M18 only. In addition, patients will undergo a physical exam (including height, weight and Tanner staging at M18 only), vital signs, extramedullary disease assessment, CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

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

Patients will undergo the following: blood collection for hematology, chemistry and CTL019 PK. Blood will be collected for flow cytometry (B and T cells, tumor cells) and RCL by VSV-G qPCR annually at M24, M36 and M48 only. Blood will be collected for [REDACTED] humoral & cellular immunogenicity at M24 and M36 only. In addition, patients will undergo a physical exam (including height, weight and Tanner staging), vital signs, extramedullary disease assessment, CNS symptom assessment and a performance status

[REDACTED]

assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

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

7.1.3.1 End of Treatment and Primary Follow-Up visit (M60 ± 14d) including premature discontinuation

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

During the EOT and Primary Follow-Up visit, patients will undergo the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B and T cells, tumor cells, and CD19 assessment), cytokines, humoral and cellular immunogenicity, [REDACTED] and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including height, weight, GVHD assessment, Tanner staging, vital signs, and extramedullary disease assessment), CNS symptom assessment, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

Following completion of the Treatment and Primary Follow-Up, patients will be followed for survival until end of study as defined in [Section 4.2 \(Section 7.1.5\)](#). Patients who discontinue or withdraw from the Treatment and Primary Follow-Up early will be asked to continue the study in the Secondary Follow-up Phase through Month 60.

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.1.3.2 Criteria for premature patient withdrawal from Treatment and Primary Follow-Up Phase

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

- Treatment failure
- Relapse after remission

[REDACTED]

- Pursuing HSCT while in remission
- Patient voluntary withdrawal from the primary follow-up

For patients who are lost to follow-up, the investigator should show “due diligence” by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.1.3.3 Relapse Evaluation

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

- a. Tumor characterization: Can be done on either blood or bone marrow with known tumor involvement of these components depending on availability of specimens, but priority is to do the majority of testing on bone marrow:
 1. Flow cytometry (B and T cells, tumor cells and CD19 assessment)
 2. Blood and bone marrow morphology
 3. Cytogenetics/ FISH/ [REDACTED]
 4. [REDACTED]
- b. CTL019 cell characterization: Must be done on both peripheral blood and bone marrow, depending on availability of specimens:
 1. PK by q-PCR and flow cytometry
 2. [REDACTED]
- c. Immunogenicity (humoral & cellular)
- d. [REDACTED]

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

7.1.4 Secondary Follow-Up Phase

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

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

During the secondary follow-up phase, patients will undergo one or more of the following at each visit according to Table 7-2: Blood collection for hematology, humoral immunogenicity,

[REDACTED]

cytokines, CTL019 transgene persistence, flow cytometry (B and T cells, tumor cells) and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including height, weight and Tanner staging), vital signs, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported. Efficacy will be assessed in patients who are still in remission until relapse. For these patients, relapse status will be assessed at each visit.

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

In addition, in the event a patient that is still in remission cannot attend any visit during the secondary follow-up, the investigator should attempt to contact the patient by phone to determine relapse status.

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

7.1.4.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study. Patients lost to follow up should be recorded as such on the CRF.

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 Novartis or health authorities.

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

7.1.5 Survival Follow-Up Phase

For all patients who complete or prematurely discontinue from the primary or secondary follow-up phase, attempts to follow-up will be made to determine survival every 3 months post-CTL019 infusion until end of study as defined in [Section 4.2](#) or patient is enrolled in the 15 year long term follow-up, whichever occurs first.

7.1.6 Long-Term Follow Up

As a single administration study, patients are followed on study for 1 year post-infusion for safety and efficacy evaluations. A long term post-study follow-up for lentiviral vector safety will continue under a separate protocol for 15 years post infusion per health authority guidelines (destination protocol).



Under the 15 year long term follow-up protocol, semiannual and annual evaluations will be performed on all patients who have received a CTL019 cell product infusion as recommended by the FDA and EMA in accordance with the relevant guidelines. All patients who either complete the study or prematurely discontinue post-CTL019 infusion will be enrolled in this destination protocol at the time of study completion/discontinuation (a separate informed consent/assent forms will be provided for this protocol). One to two times a year patients will visit the clinical site for a physical exam and medical history (including concomitant medications and adverse events) with careful attention to features possibly related to lentiviral associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, or new incidence of other hematologic disorders. In addition, labs will be drawn to evaluate routine safety endpoints, CTL019 vector persistence and RCL.

7.2 Assessment types

7.2.1 Efficacy assessments

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

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

Patients with B-cell Lymphoblastic Lymphoma will be assessed for efficacy per local investigator assessments only in accordance with Novartis guideline ([Appendix 3](#)).

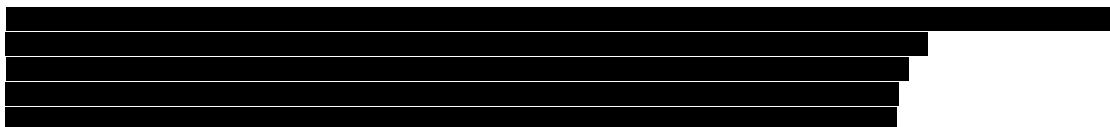
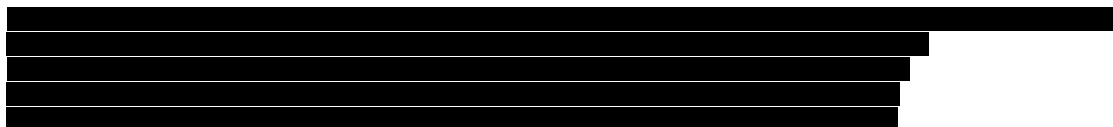


Table 7-4 Imaging or disease assessment collection plan – Primary follow-up phase

Procedure	Screening/Pre-infusion	Post-infusion Assessments
Bone marrow aspirate and biopsy for morphologic blast cell counts	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Recommended (but not required) at month 3 and 6 and as clinically indicated
Peripheral blood for morphologic blast, neutrophil and platelet cell counts	Mandated	Mandated: Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 (EOT)
Lymph node or other involved tissue aspirate or biopsy	As clinically indicated	As clinically indicated
CSF Assessment/Lumbar puncture for CNS disease	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Additional CSF assessments as clinically indicated
MRD assessments in bone marrow aspirate by flow cytometry (includes normal B cell counts and CD19 status)	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Recommended (but not required) at month 3 and 6 and as clinically indicated.
CNS Brain Imaging (CT/MRI)	As clinically indicated	As clinically indicated
Mediastinal disease assessment (chest CT scan or MRI scan)	As clinically indicated, mandatory only for Lymphoblastic Lymphoma patients	Mandated: Screening, M1. If at any time point, mediastinal disease is present by CT/MRI assessment, then follow-up CT/MRI is required to document the absence of mediastinal involvement whenever the patient meets all other criteria for complete remission.
Extramedullary disease assessment (physical exam and CNS symptom assessment)	Mandated	Mandated: Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 (EOT)
Flow Cytometry of peripheral blood (B and T cell, tumor cell, CD19 assessment)	Mandated	Mandated: Days 7, 14, and 21, and Months 1, 3, 6, 9, 12, 24, 36, 48 and 60 (EOT)



7.2.1.1 Physical examination

A targeted physical examination focusing upon sites of extramedullary disease involvement including assessments for hepatomegaly, splenomegaly, skin/gum infiltration, testicular masses and other disease manifestations are required. In addition, the physical examination will also include the assessments of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and the neurological system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Significant findings that were present prior to the signing of informed consent/assent must be included in the Medical History page on the patient's CRF. Significant findings that begin or worsen after study treatment (i.e. lymphodepleting chemotherapy) must be recorded on the Advert Even page of the patient's CRF as defined in [Section 8.1.1](#). For visits where disease response is assessed (month 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60), assessment results will be recorded on the physical exam disease response CRF page.

7.2.1.2 CNS Symptom Assessments

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

7.2.2 Safety and tolerability assessments

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

7.2.2.1 Vital signs

Vital signs include temperature, blood pressure, pulse measurements, and respiratory rate. Pulse oximetry will be measured at select visits (see [Table 7-1](#)).

7.2.2.2 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.



7.2.2.3 Performance status

Table 7-5 Karnofsky/Lansky Performance Scales

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

7.2.2.4 Tanner Staging

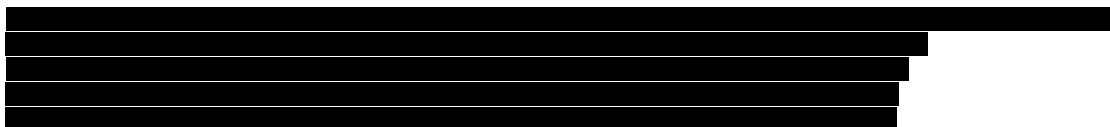
Tanner staging will be updated semiannually. If a patient is classified as Tanner Stage 5 at screening or at any point during the trial, no further Tanner staging will be required for the remainder of the trial. Female patient reproductive status (menstrual status and pregnancy information) will be updated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

7.2.2.4.1 Males

Genitalia stages:

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

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



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

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

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

Pubic Hair Stages:

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

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

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

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

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

7.2.2.4.2 Females

Breast stages:

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

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

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

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

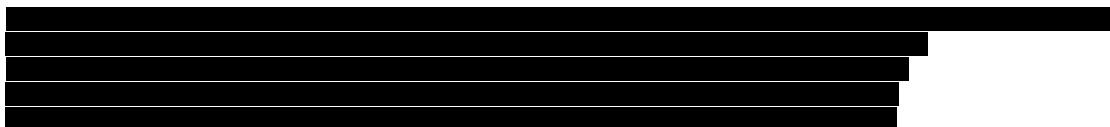
Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

Pubic Hair Stages:

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

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

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



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

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

7.2.2.5 Laboratory evaluations

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

The Investigator will evaluate the clinical significance of each applicable laboratory value outside of the reference range. This decision shall be based upon the nature and degree of the observed abnormality. Values which are considered clinically significant and/or study related to CTL019 will be noted. The Investigator may choose to repeat any abnormal result once, in order to rule out laboratory error. "NCS" will be entered on the original laboratory sheet of all laboratory values which are outside the reference range, but are judged "not clinically significant." The physician making these assessments shall date and initial each form.

Table 7-6 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin Concentration (MCHC), MCV (Mean Corpuscular Volume), Platelets, Red blood cells, White blood cells with complete differential (Basophils, Eosinophils, Lymphocytes, Atypical Lymphocytes, Monocytes, Neutrophils, Lymphoblasts, Plasma cells, Prolymphocytes, Myelocytes, Metamyelocytes, and Promyelocytes)
Chemistry	Serum Glucose (fasting or non-fasting), Blood Urea Nitrogen (BUN), Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Magnesium, Phosphorus, Lactate Dehydrogenase (LDH), [REDACTED] and Uric Acid.
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, and either leukocyte esterase or nitrites) If macroscopic panel is abnormal then perform microscopic panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR), activated Partial thromboplastin time (aPTT), fibrinogen, and D-dimer
Pregnancy screen	Serum or urine tests
Viral Serology	Hepatitis C Virus (HCV) antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs), HIV (if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines)
CSF	White Blood Cells with differential (Monocytes, Lymphocytes, Macrophages, Neutrophils, Lymphoblasts), Red Blood cells, Glucose, Protein

[REDACTED]

Test Category	Test Name
B cell and T cell levels	Peripheral blood B cell, CD4 T cell, and CD8 T cell levels (flow cytometry) (all patients after 1 year)
Additional assessments	Serum immunoglobulin levels (IgG, IgA, IgM) peripheral blood donor chimerism (prior allogeneic SCT patients only, or if unknown), bone marrow morphologic blast cell counts (flow cytometry), peripheral blood morphologic blast, neutrophil and platelet cell counts (flow cytometry)

Table 7-7 Central clinical laboratory parameters collection plan

Test Category	Test Name
MRD	MRD flow panel (bone marrow aspirate)
Flow cytometry	Bcells, CD4 T cells, CD8 T cells, [REDACTED], CD19 assessment (peripheral blood and bone marrow aspirate)
[REDACTED]	[REDACTED]
CTL019 assessments	CTL019 PK by q-PCR and/or flow cytometry (peripheral blood and bone marrow aspirate and CSF if available), [REDACTED]
[REDACTED]	[REDACTED]
RCL (VSV-G)	VSV-g q-PCR (peripheral blood)
Immunogenicity	Prevalence and Incidence of immunogenicity against CTL019 (peripheral blood and serum)
[REDACTED]	[REDACTED]

Refer to the [\[Central Laboratory Manual\]](#) for more detailed instructions for the collection, handling, and shipment of PK and [REDACTED]

7.2.3 Pharmacokinetics

Table 7-8 CTL019 pharmacokinetics by q-PCR in peripheral blood collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-8 to D-8 Enrollment/Pre-Chemotherapy	3 mL
1	D1 10 min ± 5 min post-infusion	3 mL
1	D4±1d	3 mL
1	D7±1d	3 mL
1	D11 ±1d	3 mL
1	D14±3d	3 mL
1	D21±3d	3 mL
1	D28±4d	3 mL
1	M3±14d	3 mL
1	M6±14d	3 mL
1	M9±14d	3 mL
1	M12±14d	3 mL
1	M18±14d	3 mL
1	M24±14d	3 mL
1	M30±14d	3 mL
1	M36±14d	3 mL
1	M42±14d	3 mL

[REDACTED]

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	M48±14d	3 mL
1	M54±14d	3 mL
1	M60±14d (EOT)	3 mL
1	Unscheduled PK samples related to)***	2 mL/collection
1	Unscheduled (PK samples related to safety events, relapse)	3 mL/collection

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

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

*** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible. See [Section 7.1.3](#).

Table 7-9 CTL019 pharmacokinetics by flow cytometry in peripheral blood collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume
1	W-8 to D-8 Enrollment/Pre-Chemotherapy	2 mL
1	D4±1d	2 mL
1	D7±1d	2 mL
1	D11±1d	2 mL
1	D14±3d	2 mL
1	D21±3d	2 mL
1	D28±4d	2 mL
1	M3±14d	2 mL
1	M6±14d	2 mL
1	M9±14d	2 mL
1	M12±14d	2 mL
1	M18±14d	2 mL
1	M24±14d	2 mL
1	M30±14d	2 mL
1	M36±14d	2 mL
1	M42±14d	2 mL
1	M48±14d	2 mL
1	M54±14d	2 mL
1	M60±14d (EOT)	2 mL
1	Unscheduled PK samples related to CRS	2 mL/collection
1	Unscheduled (e.g. related to safety events, at relapse)	2 mL

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

** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible. See section 7.1.3.

Table 7-10 CTL019 pharmacokinetics by q-PCR in bone marrow aspirate collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-8 to W-4 Screening	2 mL
1	D28±4d	2 mL
1	M3±14d (recommended but not required)	2 mL

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	M6±14d (recommended but not required)	2 mL
1	Unscheduled (e.g. related to safety events, at relapse)	2 mL/collection

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

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

Table 7-11 CTL019 pharmacokinetics by flow cytometry in bone marrow aspirate collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-8 to W-4 Screening	2 mL
1	D28±4d	2 mL
1	M3±14d (recommended but not required)	2 mL
1	M6±14d (recommended but not required)	2 mL
1	Unscheduled (e.g. related to safety events, at relapse)	2 mL/collection

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

Table 7-12 CTL019 pharmacokinetics by q-PCR in CSF collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume
1	W-8 to W-4 Screening	4-6 mL
1	D28±4d	4-6 mL
1	Unscheduled	4-6 mL

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

Table 7-13 Immunogenicity serum sample collection log

Treatment Period or Cycle	Day/ Scheduled Time Point**	Sample Volume
1	W-8 to D-8 Enrollment/Pre-Chemotherapy	5 mL
1	D14±3d	5 mL
1	D28±4d	5 mL
1	M3±14d	5 mL
1	M6±14d	5 mL
1	M12±14d	5 mL
1	M24±14d (Primary follow-up only)	5 mL
1	M36±14d (Primary follow-up only)	5 mL
1	Unscheduled (e.g. related to safety events, at relapse)	5mL/collection

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

Table 7-14 Immunogenicity peripheral blood sample collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-8 to D-8 Enrollment/Pre-Chemotherapy	10 mL
1	D14±3d	10 mL
1	D28±4d	10 mL
1	M3±14d (Primary follow-up only)	10 mL
1	M6±14d (Primary follow-up only)	10 mL
1	M12±14d (Primary follow-up only)	10 mL

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	M24±14d (Primary follow-up only)	10 mL
1	M36±14d (Primary follow-up only)	10 mL
1	Unscheduled (e.g. related to safety events, at relapse)	10 mL/collection

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

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

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

Day/ Scheduled Time Point*/**	Dose Reference ID	Toci Sample Number	Sample Volume (serum) (PK+PD)	CTL019 PK by qPCR Sample Number	Sample Volume (whole blood)	CTL019 PK by flow cytometry Sample Number	Sample Volume (whole blood)
D1 (5-15 minutes post infusion)	101	1	5 mL	--	--	--	--
D1 1 hour ± 15 min post infusion	101	2	5 mL	201	2 mL	601	2 mL
D2 ± 2 hours	101	3	5 mL	202	2 mL	602	2 mL
D3 ± 4 hours	101	4	5 mL	203	2 mL	603	2 mL
D7 ± 1d	101	5	5 mL	204	2 mL	604	2 mL
D1 (pre-dose; second infusion)	101	6	5 mL	205	2 mL	605	2 mL
D1(5-15 minutes post second infusion)	102	7	5 mL	--	--	--	--
D2 ± 2 hours from second infusion	102	8	5 mL	206	2 mL	606	2 mL

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

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

Unscheduled CTL019 PK sample collections related to CRS as specified in Table 7-8 and Table 7-9 will cease once PK/PD sample collections related to tocilizumab infusion commence, if applicable.

Table 7-16 Anti-cytokine therapy (other than tocilizumab) PK, CTL019 PK and sIL6R (PD) in anti-cytokine therapy treated patients during CRS

Day/ Scheduled Time Point*/**	Dose Reference ID	Anti-cytokine Rx Sample Number	Sample Volume (serum) (PK+PD)	CTL019 PK by qPCR Sample Number	Sample Volume (whole blood)	CTL019 PK by flow cytometry Sample Number	Sample Volume (whole blood)
D1 (5-15 minutes post infusion)	301	401	5 mL	--	--	--	--
D1 1 hour ± 15 min post infusion	301	402	5 mL	501	2 mL	701	2 mL
D2 ± 2 hours	301	403	5 mL	502	2 mL	702	2 mL
D3 ± 4 hours	301	404	5 mL	503	2 mL	703	2 mL
D7 ± 1d	301	405	5 mL	504	2 mL	704	2 mL
D1 (pre-dose; second infusion)	301	406	5 mL	505	2 mL	705	2 mL

Day/ Scheduled Time Point ^{*/**}	Dose Reference ID	Anti-cytokine Rx Sample Number	Sample Volume (serum) (PK+PD)	CTL019 PK by qPCR Sample Number	Sample Volume (whole blood)	CTL019 PK by flow cytometry Sample Number	Sample Volume (whole blood)
D1(5-15 minutes post second infusion)	302	407	5 mL	--	--	--	--
D2 ± 2 hours from second infusion	302	408	5 mL	506	2 mL	706	2 mL

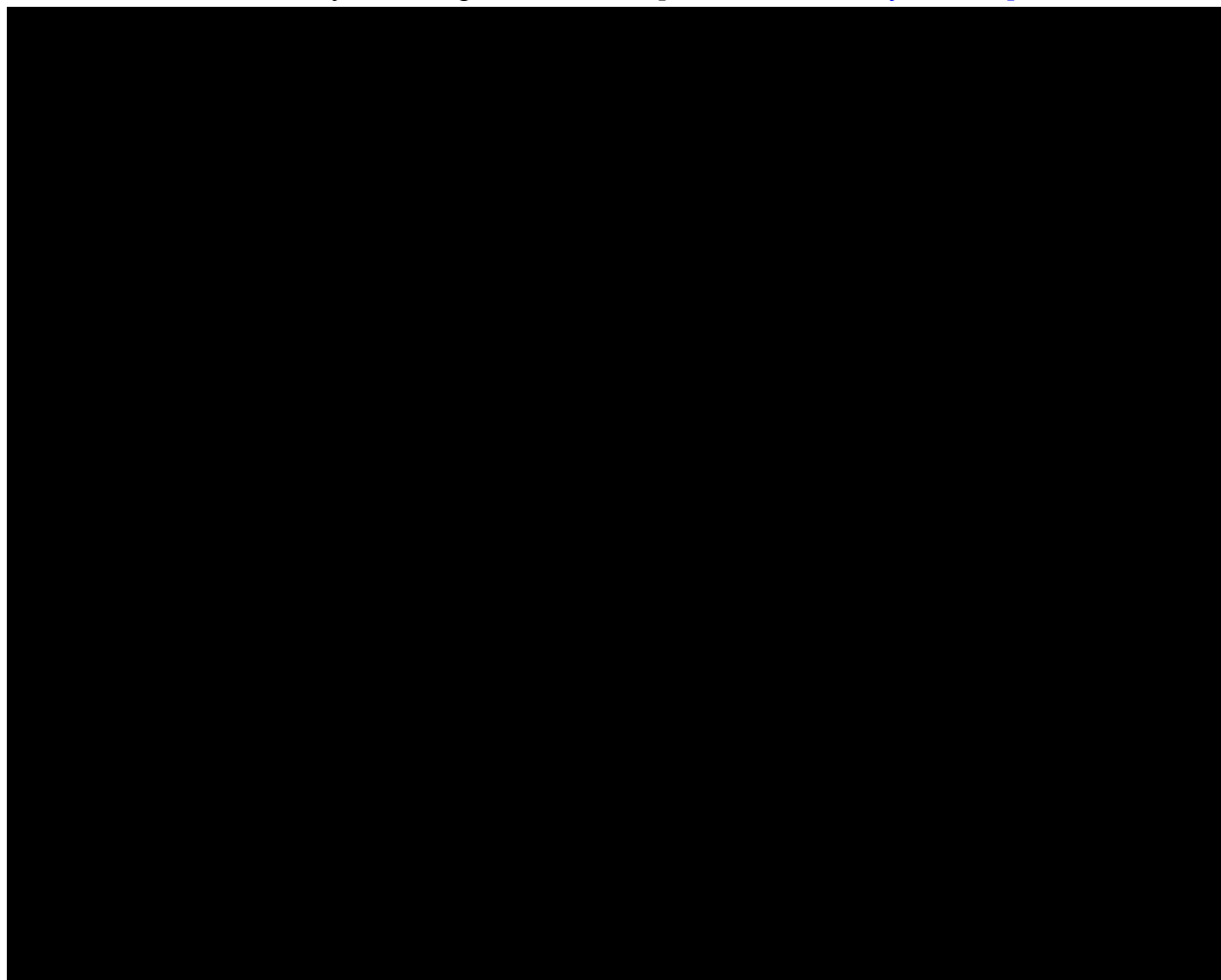
*All measurement times are relative to anti-cytokine therapy administration unless otherwise specified. A serum sample collected at D1 for cytokine analysis (see [Table 7-17](#)) would serve as the baseline sample.

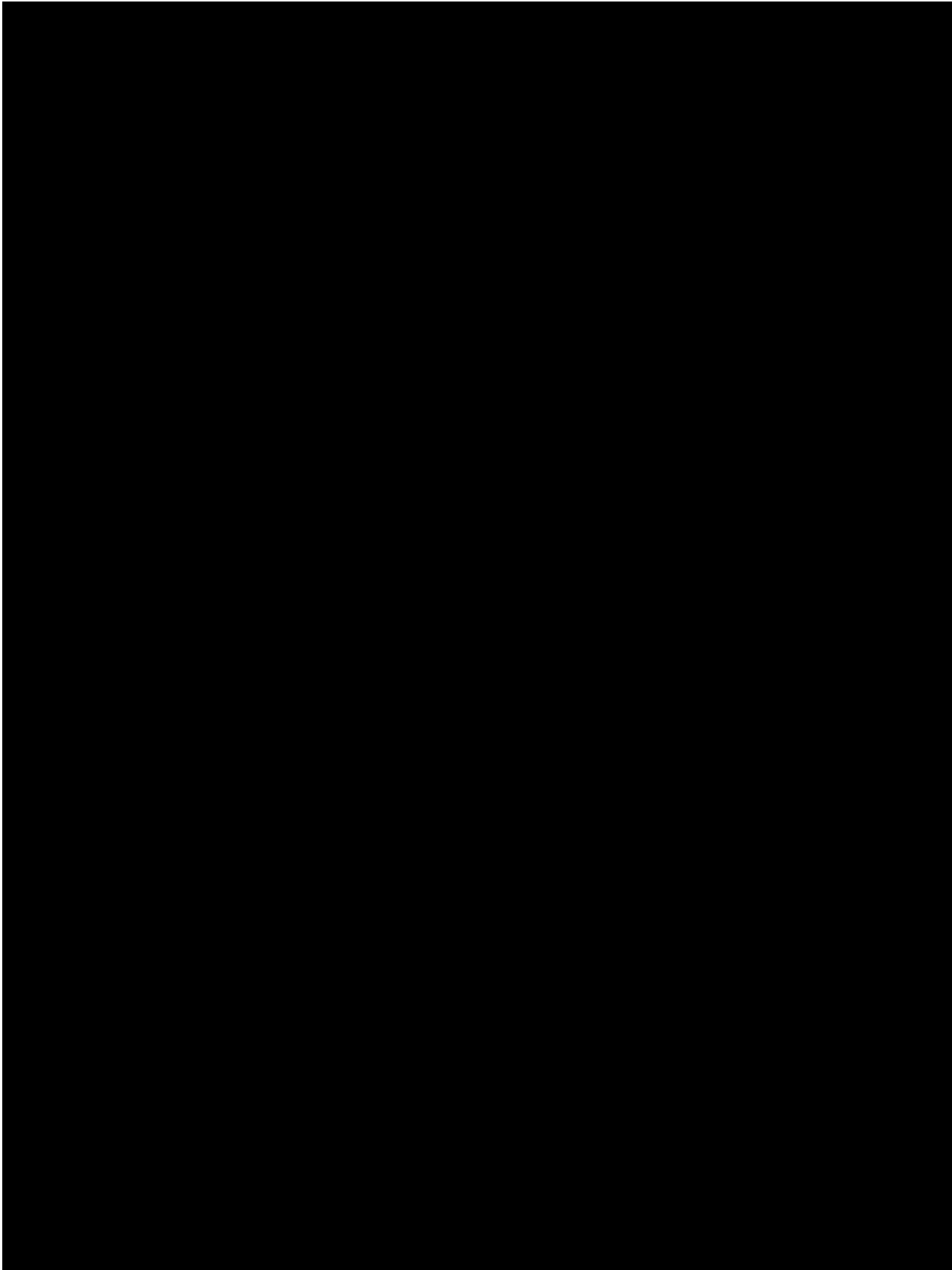
**Samples may be collected as needed dependent upon administration of anti-cytokine therapy, if clinically feasible.

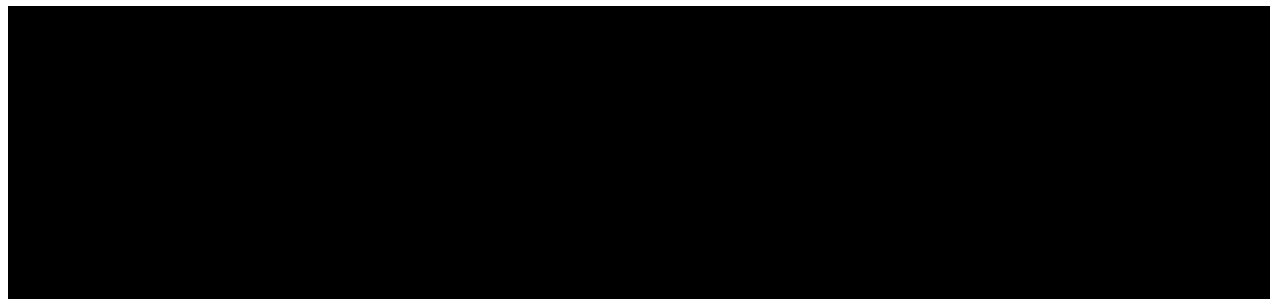
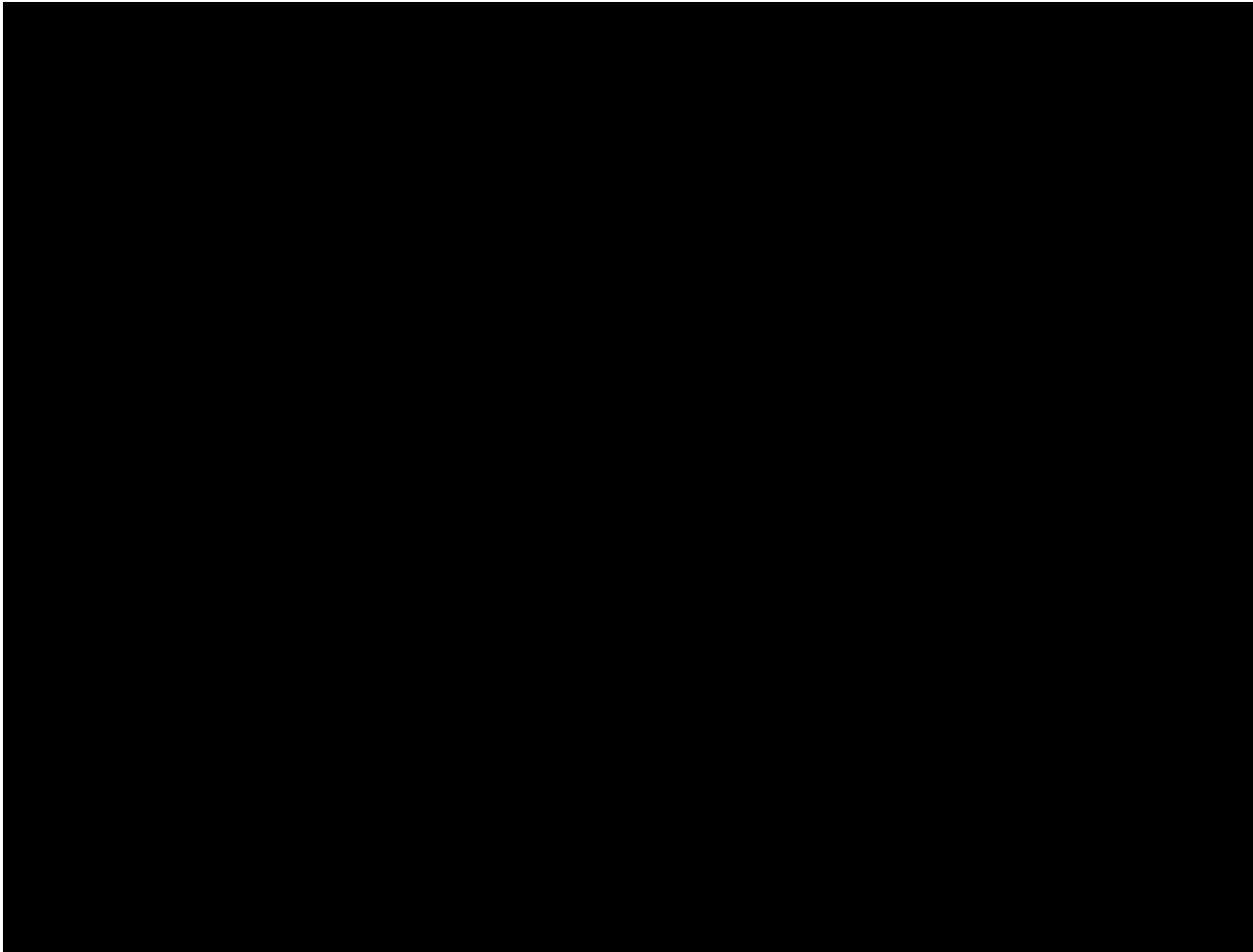
Unscheduled CTL019 PK sample collections related to CRS as specified in [Table 7-8](#) and [Table 7-9](#) will cease once PK/PD sample collections related to anti-cytokine therapy administration commence, if applicable.

7.2.3.1 Analytical method

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







7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Not applicable.



8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions

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

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

8.1.2 Reporting

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

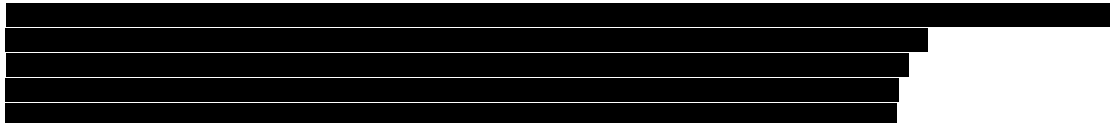
- All infections
- All clinical AEs Grade ≥ 3
- All laboratory abnormalities deemed clinically significant by the investigator
- All AEs related to a study procedure
- All AEs leading to study discontinuation

If a patient is simultaneously enrolled in the active phase (start of apheresis until 24 hours thereafter) of the Novartis [\[CTL019B2206\]](#) leukapheresis protocol and this treatment protocol, collection and reporting of adverse events during this overlapping period should follow the CTL019B2206 safety reporting criteria. Therefore during this overlap period, AEs should only be reported to the CTL019B2206 protocol, and not on the CTL019B2205J protocol. After completion of the active phase on CCTL019B2206, reporting of SAEs should follow the criteria of the respective treatment protocol the patient is participating in.

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

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

- Events leading to death
- Events related to a study procedure
- Infections:



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

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

Adverse events will be assessed according to the Medical Dictionary for Regulatory Authorities (MedDRA) version 16.1 and the Common Terminology Criteria for Adverse Events (CTCAE version 4.03, with the exception of CRS, which will follow [Table 6-1](#). If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through a Death form.

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

1. The severity grade (CTCAE v. 4.03 Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No; Yes, investigational treatment; Yes, the study treatment (non-investigational); Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, temporarily interrupted, permanently discontinued, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)



6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event is defined as in [Section 8.2.1](#)

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

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method should not be reported as a serious adverse event.

Modified data capture for inpatient/in hospital events

A significant number of CTL019 treated patients will require multiple days of inpatient and/or ICU care. These side effects are mostly due to CRS and MAS, although there may be some contribution from the preceding lymphodepleting chemotherapy (neutropenia fever, cytopenias). CRS/MAS toxicity is an ‘on-target’ effect resulting from the expected CTL019 cell expansion, activation and tumor cell killing.

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

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

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

8.1.3 Laboratory test abnormalities

8.1.3.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a



sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.1.4 Adverse events of special interest

Adverse events of special interest (AESI) are described in [Table 10-4](#) below. The current search criteria of AESI are based on limited experience from ongoing clinical studies without an accurate assessment of causality. The search criteria of the AESI may be updated prior to database lock for primary analysis reporting. Based on current clinical experience, AESI typically occur and resolve within 8 weeks of CTL019 infusion in ALL patients.

8.2 Serious adverse events

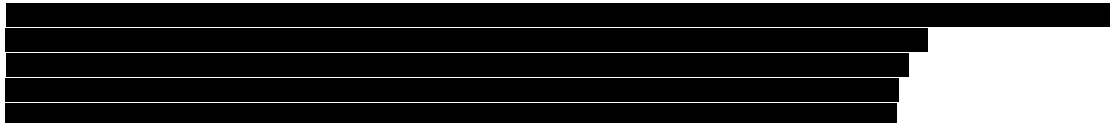
8.2.1 Definitions

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

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

8.2.2 Reporting

Any SAEs experienced during the screening/pre-treatment phase (from the time of patient providing informed consent/assent until the patient begins study-related treatment) should



only be reported Novartis and be captured if the CRF/safety database if the event meets at least one of the following criteria:

- All events leading to death.
- All pulmonary or cardiac abnormalities
- All infections
- All events related to a study procedure
- Any AE reportable for this study period that also meets criteria for serious

Substantial change in the status of the patient that the investigator deems may have a potential impact during lymphodepletion and CTL019 infusion or precludes the patient from proceeding to study treatment (e.g. GVHD, rapid progression of malignancy, marked decline in clinical status)

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

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

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

- Events leading to death
- Events related to a study procedure
- Infections:
 - Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria:
 - Require anti-infective treatment OR
 - Lead to significant disability or hospitalization OR
 - Need for surgical or other intervention
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of other hematologic disorder
- Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy
- Positive RCL test result
- Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene
- New malignancy (T-cell & non T-cell), other than the primary malignancy
- Progressive multifocal leucoencephalopathy (PML)



- Hepatitis B reactivation

In addition, at the specific request of the FDA, the following SAEs will be reported in an expedited manner to the FDA:

- All occurrences of CRS Grade ≥ 3
- All deaths regardless of attribution following lymphodepleting chemotherapy and/or CTL019 infusion and within 30 days of receiving CTL019 infusion
- Death attributed to CTL019 occurring 30 days post CTL019 infusion

Any SAEs experienced after the Month 60 (EOT) visit should only be reported to the Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and send the completed, signed form by fax or email within 24 hours to Novartis.

The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, Novartis may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.



8.4 Pregnancies

No data are currently available to determine the duration of contraception after receiving CTL019. CTL019 is within Pregnancy Category C. Animal reproduction studies have not been conducted with CTL019. It is also not known whether CTL019 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Women regardless of age that may have child-bearing potential (defined as all women physiologically capable of becoming pregnant) are recommended to continue contraception until CAR cells are no longer present in blood as measured by PCR and for a minimum of 12 months from CTL019 infusion. Women who are not yet of reproductive potential are also to agree to use acceptable forms of contraception when they reach reproductive potential. Male participants must use highly effective methods of contraception for a period of 1 year after CLT019 infusion. Highly effective contraception methods include:

- a. 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
- b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- c. 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.
- d. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
- e. Use of intrauterine devices are excluded due to increased risks of infection and bleeding.
- f. In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment.

Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months (i.e. have had no menses) or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception. Women who are not yet of reproductive potential are to agree to use acceptable forms of contraception when they reach reproductive potential if within 1 year of CTL019 or if CAR cells are present in the blood by PCR. Acceptable documentation includes written or oral documentation communicated by clinician or clinician's staff of one of the following:

- a. Demographics show age <11
- b. Physical examination indicates Tanner Stage 1
- c. Physician report/letter
- d. Operative report or other source documentation in the patient record
- e. Discharge summary
- f. Follicle stimulating hormone measurement elevated into the menopausal range



To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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. Pregnancies will be followed for pregnancy outcome. In the case of live birth the newborn will be followed up until 6 months of age to detect any developmental issue or abnormality that would not be seen at birth. Pregnancy outcomes must also be collected for the female partners of any males who received CTL019 in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to Novartis. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the CTL019 transduced cells to any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

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

8.6 Data Monitoring Committee

Prior to the transfer of the study from UPenn IND to Novartis IND, an independent Data Safety Monitoring Board (DSMB) had reviewed safety and efficacy data up until August 2015. After the transfer of the IND is complete, an independent Novartis Data Monitoring Committee will oversee the safety data for the study.

The DMC will be responsible for reviewing the safety data of the patients treated in the study. The DMC will consist of members who are not involved in patient recruitment or trial conduct, with at least two oncologists (at least one pediatric hematologist/oncologist) and one biostatistician. Safety reviews will occur every six months, unless otherwise requested by the Chairman of the DMC. Additional meetings will be held at the request of the DMC or Novartis' request, or in the event that significant safety issues arise. Detailed recruitment status and interim safety reports will be provided to the DMC on a regular basis.

Further details regarding the constitution of the DMC and its specific roles will be outlined in the DMC charter.

8.7 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, Novartis representatives from the Clinical Trial team. . The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as



appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules.

The SC will meet regularly, approximately every 3 months. Documentation of these meetings will be maintained in the Master Study File. Actionable outcomes and recommendations will be sent to all participating sites for local reporting.

The details of the role of the Steering Committee will be defined in a Steering Committee charter.

8.8 Independent Review Committee (IRC)

An IRC will be established to review data related to disease response assessment and determine remission and relapse for the primary analysis in acute lymphoblastic leukemia patients. An IRC charter will detail the IRC data flow and review process in alignment with the response definitions in [Appendix 1](#). Patient management will be based upon local investigator assessments. The designation of remission and relapse for the primary analysis and other related secondary efficacy endpoints will be based only on the evaluations made by the IRC. Details regarding the constitution of the IRC and its specific roles will be documented in the IRC charter agreed upon between Novartis and the IRC before initiation of any IRC reviews.

9 Data collection and management

9.1 Data confidentiality

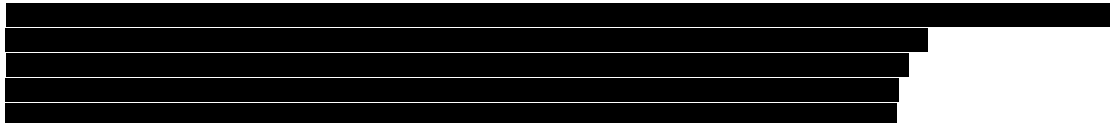
Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

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

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

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

Prior to entering key sensitive personally identifiable information (patient initials and exact date of birth), the system will prompt site to verify that this data is allowed to be collected. If



the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit patient initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation at a site initiation visit, Novartis personnel or designee will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. 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

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

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

9.4 Database management and quality control

Novartis or designee will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.



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

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

10 Statistical methods and data analysis

Data from all participating centers will be combined.

The primary analysis will be performed when at least 50 acute lymphoblastic leukemia or lymphoblastic lymphoma patients (including 40 patients less than 18 years of age) have received CTL019 infusion and completed 6 months from study day 1 infusion or discontinued earlier. The additional data for any patients continuing past this time will be further summarized in the final Clinical Study Report (CSR) once all patients complete the study.

10.1 Analysis sets

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

Tables and listings will be presented by acute lymphoblastic leukemia and lymphoblastic lymphoma separately, within the single treatment arm of CTL019. If there are no more than 5 lymphoblastic lymphoma patients treated, data for these patients will be summarized primarily via listings.

10.1.1 Screened Set

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

10.1.2 Enrolled Set

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

10.1.3 Full Analysis Set

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

10.1.4 Safety Set

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



10.1.5 Per-Protocol Set

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

Major protocol deviations leading to exclusion from the PPS include:

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

In addition, patients who receive a dose less than the minimum target dose (2×10^6 CTL019 transduced cells/kg body weight) will also be excluded.

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

10.1.6 Pharmacokinetic analysis set

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

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

10.2 Patient demographics/other baseline characteristics

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

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

Patients will be classified by the allogeneic SCT and residual donor engraftment status into one of the following categories:

- Relapsed after prior allogeneic SCT with any degree of residual donor engraftment
- Relapsed after prior allogeneic SCT with no residual donor engraftment
- No prior allogeneic SCT

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

- Primary refractory: If patient never had a morphologic complete remission (CR) prior to the study
- Relapse without SCT: If patient has not had SCT, had a CR from other therapy and relapsed prior to the study
- Relapse after SCT: If patient has had and relapsed after SCT prior to the study



10.3 Treatments (study treatment, concomitant therapies, compliance)

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

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

10.4 Primary objective

The primary objective of the study is to evaluate the efficacy of CTL019 therapy in acute lymphoblastic leukemia patients and separately in lymphoblastic leukemia patients as measured by overall remission rate (ORR) during the 6 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) in the FAS population. The primary analysis will be based on the IRC assessment for acute lymphoblastic leukemia patients, and based on local investigator's assessment for lymphoblastic lymphoma patients. In addition, sensitivity analysis will be performed using the local investigator response assessments instead of the IRC assessment for acute lymphoblastic leukemia patients.

10.4.1 Variable

The primary endpoint is the ORR during the 6 months after CTL019 administration, as determined by IRC assessment for acute lymphoblastic leukemia patients and as determined by local investigator's assessment for lymphoblastic lymphoma patients.

The ORR is defined as the proportion of patients with a best overall disease response of CR or CRi, where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until the start of new anticancer therapy. Best response will be assigned according to the following order:

- CR
- CRi
- CR or CRi with residual mediastinal disease (for lymphoblastic lymphoma patients only)
- No response (NR)
- Unknown

The disease response criteria for ALL patients are outline below in Table 10-1. See also Appendix 1 for details. (Please note: For lymphoblastic lymphoma patients, all criteria below plus those listed in Table 10-2, Appendix 2, Table 14-5 must be met.)



Table 10-1 Definition of CR, CRi and relapse at a given evaluation time in Acute Lymphoblastic Leukemia patients (excluding Lymphoblastic Lymphoma patients)

Response category	Definition
Complete remission (CR)	<p>All the following criteria are met:</p> <p>Bone marrow</p> <ul style="list-style-type: none"> • Trilineage Hematopoiesis (TLH) and < 5% blasts <p>Peripheral blood</p> <ul style="list-style-type: none"> • Neutrophils > $1.0 \times 10^9/L$, and • Platelets > $100 \times 10^9/L$, and • Circulating blasts < 1% <p>Extramedullary disease</p> <ul style="list-style-type: none"> • No clinical evidence of extramedullary disease (by physical exam and CNS symptom assessment), and • If additional assessments (e.g. CSF assessment by LP, CNS imaging, biopsy, etc.) are performed, results must show remission status <p>Transfusion independency</p> <ul style="list-style-type: none"> • No platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	<p>All criteria for CR as defined above are met, except that the following exist:</p> <ul style="list-style-type: none"> • Neutrophils $\leq 1.0 \times 10^9/L$, or • Platelets $\leq 100 \times 10^9/L$, or • Platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Relapsed Disease	<p>Only in patients who obtained a CR or CRi:</p> <ul style="list-style-type: none"> • Reappearance of blasts in the blood ($\geq 1\%$), or • Reappearance of blasts in bone marrow ($\geq 5\%$), or • (Re-)appearance of any extramedullary disease after CR or CRi

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

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

Therefore, following initial achievement of CR/CRi, patients will be considered to have maintained a clinical CR/CRi if the patient has no evidence of extramedullary disease (by physical exam and CNS symptom assessment) and circulating blasts in peripheral blood are <1%. In order for the best ORR to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the



initial achievement of CR or CRi. Please note, if additional assessments (e.g. bone marrow, CSF assessment by LP, CNS imaging, biopsy, etc.) are performed in the same evaluation for disease response evaluation purpose, they will also need to show remission status.

The additional disease response criteria for lymphoblastic lymphoma patients are outline below in [Table 10-3](#). See also [Appendix 2](#) for more details.

Table 10-2 Additional definition of remission and relapse at a given evaluation time for Lymphoblastic Lymphoma patients

Response category	Definition
Complete remission (CR)	All the criteria for ALL are met, and in addition CR for mediastinal disease.
Complete remission with incomplete blood count recovery (CRi)	All the criteria for ALL are met, and in addition CR for mediastinal disease.
CR or CRi with residual mediastinal disease	All criteria for CR or CRi as defined above are met, except that mediastinal disease as defined by CRu or PR is observed.
Relapsed Disease	Same criteria for ALL, and in addition mediastinal relapse will also indicate relapse for LBL.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be based on statistical testing in acute lymphoblastic leukemia patients and descriptive analysis in lymphoblastic lymphoma patients. In addition, it will be summarized descriptively in all patients combined.

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

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

The primary efficacy endpoint, ORR will be analyzed at the interim look and final look of a group sequential design based on the data observed in the FAS. The ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals with coverage level determined by the O'Brien-Fleming type α -spending approach according to Lan-DeMets as implemented in East 5.4 (Lan and DeMets, 1983). The study will be considered successful if the lower bound of the 2-sided 95% exact confidence interval for ORR is greater than 20%, so that the null hypothesis that the ORR is less than or equal to 20% can be rejected.

In lymphoblastic lymphoma patients and in all patients combined, the ORR will be summarized descriptively together with 95% CIs if appropriate.

Tables and listings will be presented by acute lymphoblastic leukemia and lymphoblastic lymphoma separately, as well as one treatment arm of CTL019.

In addition, the percentage of patients who achieve CR or CRi at Day 28 +/- 4 days will also be summarized. Response will also be summarized by baseline tumor burden (MRD, extramedullary disease, etc.).



10.4.3 Handling of missing values/censoring/discontinuations

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

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

10.4.4 Supportive analyses

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

10.4.4.1 Subgroup analysis

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

- Age: <10 years, ≥10 years to <15 years, ≥15 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: Asian, Black, Caucasian, Native American, Other, Pacific Islander, Unknown
- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- Prior response status: Primary refractory, relapse without SCT, relapse from SCT
- Eligibility for SCT: Eligible for SCT, ineligible for SCT
- Baseline bone marrow tumor burden: Low (defined as either morphologic or MRD result is <50% and neither ≥50%), High (defined as either morphologic or MRD result is ≥50%)
- Baseline extramedullary disease presence: Yes, No
- Philadelphia chromosome/BCR-ABL: Positive, Negative
- Mixed-Lineage Leukemia (MLL) rearrangement: Yes, No
- Hypoploidy: Yes, No
- BCR-ABL1-like: Yes, No
- Complex Karyotypes (≥5 unrelated abnormalities): Yes, No

The rationale for performing subgroup analyses are as follows:

- Age, gender, race and ethnicity are demographic factors that are typically requested by health authorities to assess internal consistency of the study results.
- Prior response status is a key prognosis factor due to potentially higher rates of treatment related morbidity in patients who have relapsed following allogeneic SCT.
- Baseline bone marrow tumor burden and extramedullary disease presence can be important indicators of overall disease burden, which is a potential predictive factor
- BCR-ABL, MLL rearrangement, hypoploidy and BCR-ABL1-like gene signatures and complex karyotype (≥ 5 unrelated abnormalities) are high risk factors for ALL. Patients with these high risk factors have poorer diagnosis ([Harrison et al 2010](#); [van der Veer et al 2013](#); [NCCN v1 2013](#)). In case there are very few patients with these high risk mutations individually, analysis may be performed for patients with any of these high risk mutations versus those who do not.



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

10.5 Secondary objectives

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

10.5.1 Key secondary objective(s)

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

10.5.2 Other secondary efficacy objectives

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

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

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

The percentage of patients who achieve CR or CRi at Month 6 without SCT (post CTL019 infusion) between CTL019 infusion and Month 6 response assessment, among all patients in the FAS, will be summarized along with exact 95% Confidence Interval (CI). In addition, the percentage among patients who achieved CR or CRi will also be summarized. The time of proceeding to SCT is defined as the time of commencing the conditioning regimen as required for hematopoietic SCT. This definition applies to all analyses.

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

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

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

10.5.2.3 Duration of remission (DOR)

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

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

- Ongoing without event
- Lost to follow-up



- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Event after at least two missing scheduled disease assessments

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

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

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

The proposed analyses for DOR are summarized in Table 10-3 below. Method 1 will be considered as the main analysis for DOR. Additional analyses may be considered.

Table 10-3 Analyses of duration of response (DOR)

	Death due to reason other than the underlying disease	SCT after remission
Method 1	Censor at last adequate tumor assessment	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	Competing risk analysis	Ignore SCT

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

For Method 1 and Method 2, the distribution function of DOR will be estimated using the KM method. The median DOR along with 95% confidence intervals will be presented if appropriate.

For Method 3 and Method 4, the CIF is used to estimate the probability of the event of interest in the presence of the competing risks (Kim 2007).

If a considerable number of patients receive SCT while in remission after CTL019 infusion, then exploratory analyses may be performed on patients who achieve CR/CRi after CTL019 infusion to assess the effect of SCT on DOR. Baseline disease characteristics and post-baseline factors (e.g. time to CR/CRi, minimal residual disease) that may be correlated with the decision to receive SCT and with DOR will be identified. A Cox model with SCT as a time dependent covariate and potential confounding factors as additional covariates may then



be explored in patients who achieve CR/CRi after CTL019 infusion. The hazard ratio (SCT v/s No SCT after CR/CRi) estimate along with its 95% confidence interval will be provided. Additional exploratory analyses may be considered to account for the confounding factors.

10.5.2.4 CR or CRi with MRD negative bone marrow

The percentage of patients who achieved BOR of CR or CRi with MRD negative bone marrow (performed by central laboratory with sensitivity of detection of 0.01%) during the 6 months after CTL019 administration among all patients in the FAS population will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. Additional analysis will be done to summarize this percentage among all patients with BOR of CR or CRi. See [Appendix 1](#) for details of determination of MRD negativity.

The percentage above will be also summarized among all patients who achieved BOR of CR or CRi.

In addition, quality of response using MRD disease assessments before treatment, at day 28 +/- 4 days after treatment will be described.

10.5.2.5 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 (also see below for handling SCT)
- Event after at least two missing scheduled disease assessment

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

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

10.5.2.6 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 no response in the study and discontinuation from the study due to any of the following reasons:

[REDACTED]

- Adverse event (including abnormal laboratory values or abnormal test procedure results)
- Lack of efficacy or progressive disease
- New anticancer therapy

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

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

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

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

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

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

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

10.5.2.8 Response at Day 28 +/- 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 % Confidence Interval (CI).

10.5.2.9 Impact of baseline tumor burden on response

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



10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

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

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

- Pre-infusion period: from day of patient’s informed consent/assent to the day before infusion of CTL019
- Post-infusion period: starting at day of CTL019 infusion

10.5.3.2 Adverse events (AEs)

Reporting of adverse events will be based on MedDRA and CTCAE version 4.03.

Summary tables for adverse events have to include only AEs that started or worsened during the post-infusion period, i.e. the **CTL019 treatment-emergent** AEs. However, all safety data (including those from the pre-infusion period) will be listed and those collected during the pre-infusion period are to be flagged.

The incidence of CTL019-treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, preferred term, severity (based on CTCAE grades), and relation to study treatment. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of Common Toxicity Criteria (CTC) Grade 3 and 4 AEs will be summarized separately.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Adverse events of special interest (AESI) are described in [Table 10-4](#) below. The current search criteria of AESI are based on limited experience from ongoing clinical studies without an accurate assessment of causality. The search criteria of the AESI may be updated prior to reporting. AESI that occur within 8 weeks of the CTL019 infusion will be summarized by group term and preferred term.

Table 10-4 Adverse events of special interest (AESI) search criteria

AESI group term	MedDRA term	Type
Syndromes	Cytokine Release Syndrome	PT
	Histiocytosis haematophagic	PT
	Tumor Lysis Syndrome	PT
Cytokine Release Syndrome Symptoms	Pyrexia	PT
	Myalgia	PT
	Hypotension	PT
	Dyspnea	PT
	Tachypnea	PT
	Capillary Leak Syndrome	PT
	Hypoxia	PT
	Organ Failure	PT
	Acute Respiratory Distress Syndrome	PT



AESI group term	MedDRA term	Type
Tumor Lysis Syndrome Symptoms	Hyperkalemia	PT
	Hyperphosphatemia	PT
	Hyperuricemia	PT
	Hypocalcemia	PT
Histiocytosis Haematophagic Symptoms	Splenomegaly	PT
	Marrow depression and hypoplastic anemias	HLT
	Hemolysis	PT
	Disseminated intravascular coagulation	PT
	Blood triglycerides increased	PT
Organ Dysfunction	Hepatic enzymes and function abnormalities	HLT
	Renal Failure and Impairment	HLT
	Confusion and disorientation	HLT
Allergic Reaction	Infusion related reaction	PT

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE, the study's biostatistics and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- shift tables using CTCAE grades to compare baseline to the worst post-infusion value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

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

10.5.3.4 Immunogenicity

Humoral immunogenicity assessment will include prevalence of immunogenicity (subjects with pre-existing antibodies that bind to CTL019), incidence of immunogenicity (subjects with treatment-induced or treatment-boosted antibodies that bind to CTL019), together with antibody titers. Data will be further fractionated to determine proportion of subjects who make transient versus sustained antibody responses. The assay for humoral immunogenicity will be a cell-based assay, detecting antibodies that bind to a Jurkat cell line transfected with the CTL019 construct. This cell line stably expresses the complete CTL019 sequence and can be used to detect antibodies that bind to any epitope on the extracellular domain of the protein. Cellular immunogenicity assessment will include percentage of CD4+ and CD8+ T cells specific for CTL019.



10.5.3.5 Derivation of a score to predict cytokine release syndrome

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

10.5.3.6 Soluble Immune factors

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

[REDACTED]

10.5.3.7 B-cell and T-cell levels

The levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion will be described. Malignant and normal B cell populations will be listed and summarized by patient and time point.

It is anticipated that all patients who achieve complete remission will exhibit B-cell aplasia. Timing of B-cell recovery (i.e. when normal B-cell becomes detectable again after patients achieving complete response) will be summarized.

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

[REDACTED]

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

10.5.3.8 Other safety data

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10.5.3.9 Safety subgroup analysis

Key safety summaries for adverse events regardless of relationship to study drug by System, Organ, Class (SOC) and PT, and adverse events of special interest will be repeated on the Safety Set in the following subgroups:

- Age: <10 years, ≥10 years to <15 years, ≥15 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: Asian, Black, Caucasian, Native American, Other, Pacific Islander, Unknown
- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- Prior response status: Primary refractory, relapse without SCT, relapse from SCT
- Prior SCT therapy and residual donor engraftment status: Prior SCT with any degree of residual donor engraftment, SCT without residual donor engraftment, or no prior SCT.

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

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

10.5.4 Pharmacokinetics

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

- CTL019 transgene levels as measured by q-PCR
- [REDACTED]

The PK parameters listed in [Table 10-5](#) along with other relevant PK parameters will be estimated from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix[®] (Pharsight, Mountain View, CA). All concentrations below the limit of quantitation or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics. For the calculation of the PK parameters, a zero value will be imputed for the values below the limit of quantification after the administration and during the expansion phase. The values below the limit of quantification during the elimination phase will not be imputed and will be considered as missing.

Table 10-5 Noncompartmental pharmacokinetic parameters

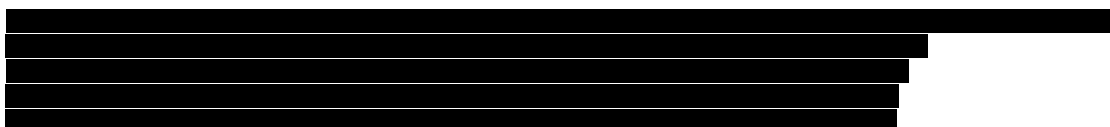
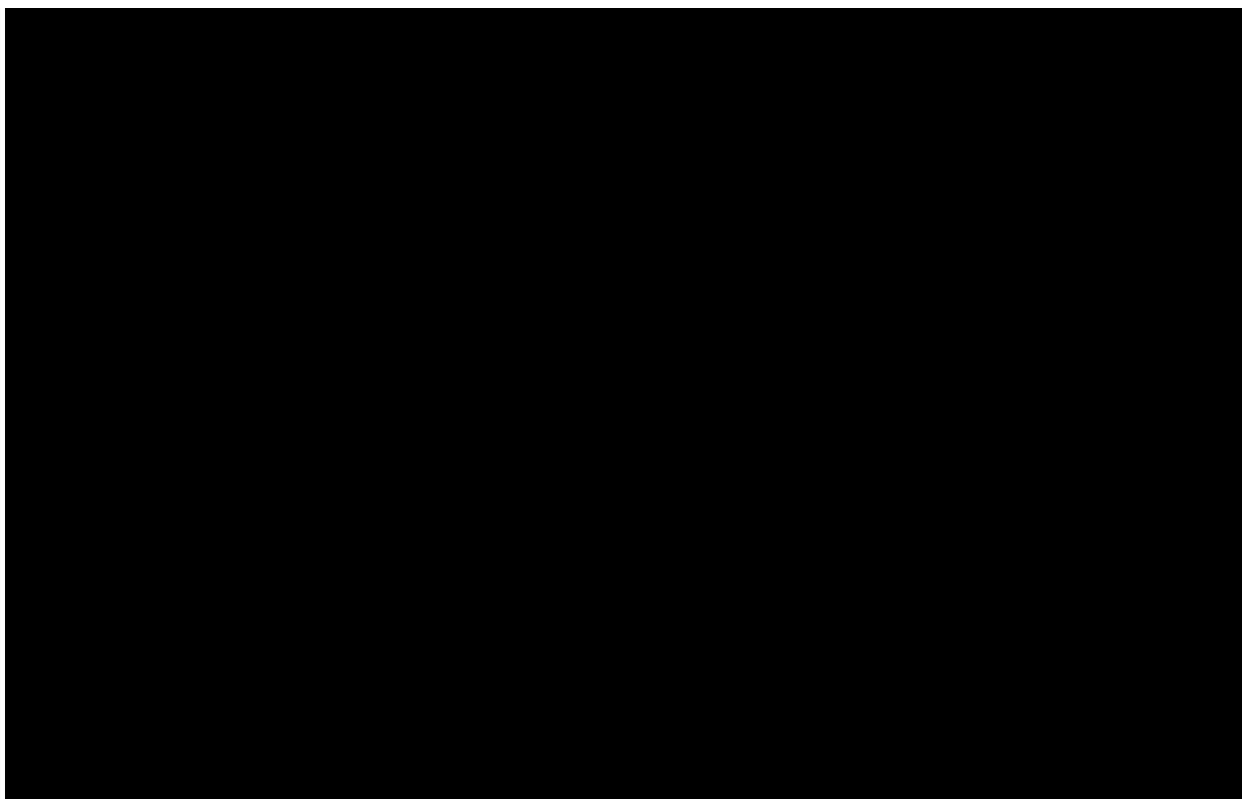
AUC 0 - Tmax	The AUC from time zero to T _{max} in peripheral blood (% or copies/μg x days x volume-1)
AUC Tmax - 28d or M3	The AUC from time Tmax to day 28 and M3 or other disease assessment days, in peripheral blood ((% or copies/μg x days x volume-1)
AUC 0 - 28d or M3	The AUC from time zero to day 28 and M3 or other disease assessment days, in peripheral blood (% or copies/μg x volume-1)
Cmax	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (% or copies/μg x volume-1)

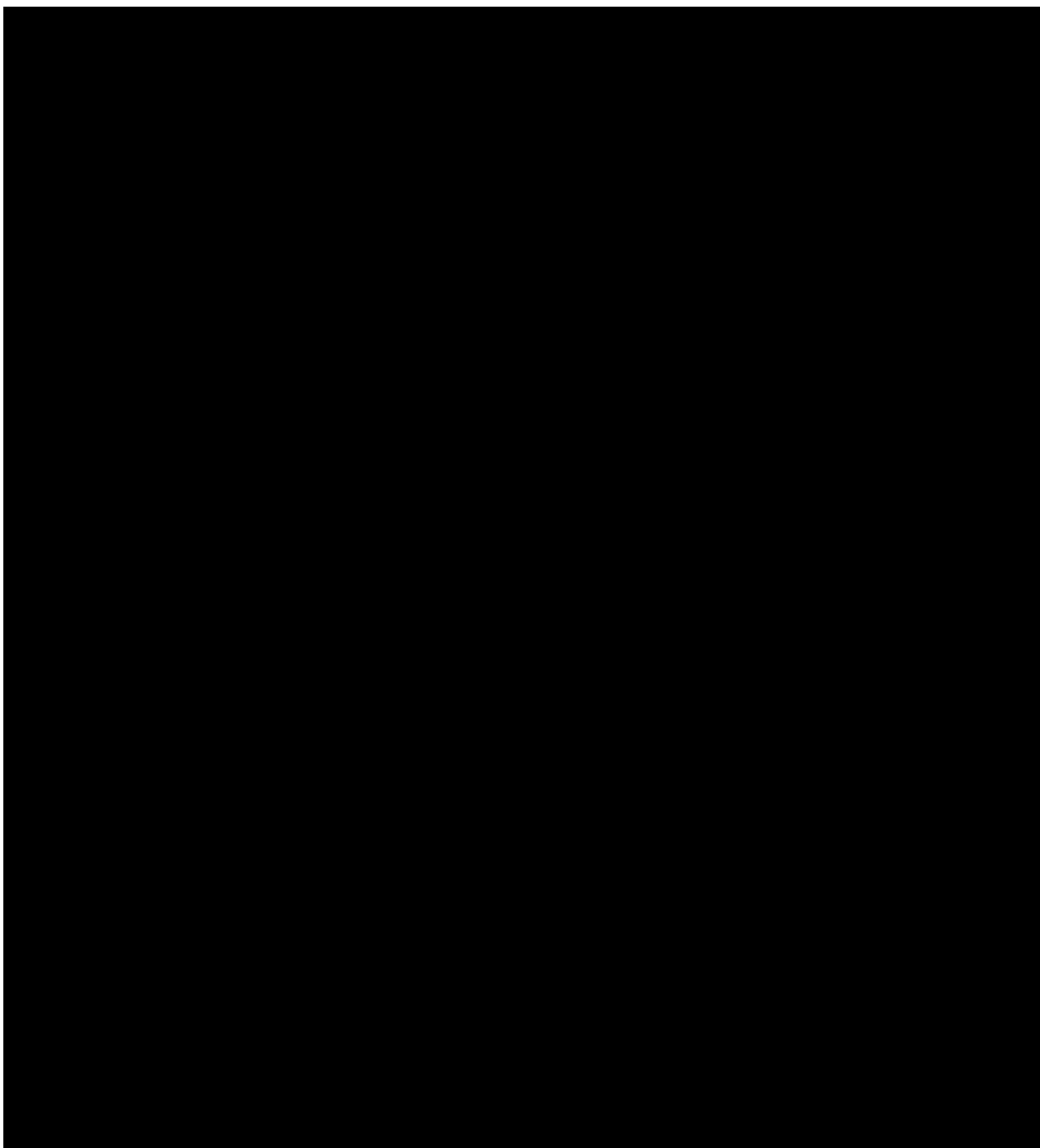
[REDACTED]

Tmax	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
T1/2	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
Ci	Initial concentration in peripheral blood following infusion ($\mu\text{g} \times \text{volume}^{-1}$) (only applicable for qPCR)
(Cmax / Ci)	In vivo CTL019 T-cell expansion in peripheral blood (using ratio of Cmax to Ci (only applicable for qPCR)
TLOG	Duration of time patient concentration levels are at or above the limit of quantitation (LOQ) for a given assay (days)
MRTlast	Mean residence time from the time of dosing to the time of the last measurable concentration in peripheral blood (days).

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

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





10.7 Interim analysis

The trial will be transferred under Novartis IND from UPenn IND. After the IND transfer, all CTL019 products will be manufactured according to the Novartis CMC process. The trial was initially conducted under the UPenn IND with CTL019 product manufactured according to the UPenn CMC process. From protocol amendment 2 going forward, the trial is transferred under Novartis IND. After the IND transfer, all CTL019 products will be manufactured according to the Novartis CMC process.



An interim analysis is planned when all patients who were treated with UPenn manufactured CTL019 product and have completed 6 months from study day 1 infusion or discontinued earlier. Only acute lymphoblastic leukemia patients will be treated with UPenn manufactured CTL019 products. The interim analysis will be performed in the acute lymphoblastic leukemia patients by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis of ORR being greater than 20% at overall one-sided 2.5% level of significance.

Approximately 30 patients will be included in the interim analysis and approximately 45 patients will be included in the final analysis in acute lymphoblastic leukemia patients. The study will not be stopped for outstanding efficacy at the interim analysis regardless of the interim result.

An α -spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in East 5.4, will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983).

Based on the choice of α -spending functions described above, if the interim analysis is performed exactly with 30 patients, the lower bound of the 2-sided 98.79% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of $13/30 = 43\%$ is needed to claim success at interim. At the final analysis, 2-sided 95.37% exact CI will be used correspondingly. As a result, an ORR of $16/45 = 35\%$ will be needed to claim success at final analysis.

In case the actual number of patients at the interim analysis cut-off date is not exactly equal to 30 patients, the efficacy boundaries will need to be re-calculated based on the actual number of patients using the pre-specified α -spending functions. The efficacy boundary at the final analysis will be based on the actual number of patients and the alpha already spent at the interim analysis. If the number of patients in the final analysis deviates from the expected n, the final analysis criteria will be determined so that the overall significance level across all analyses is maintained at one-sided 0.025.

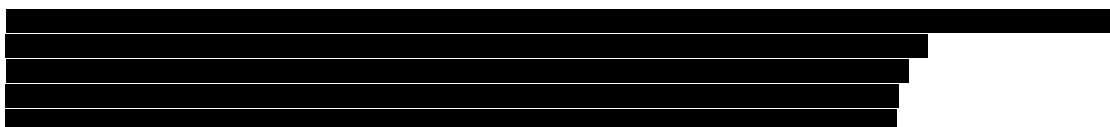
Statistical properties of the group sequential design are summarized in Table 10-6 below.

Table 10-6 Simulated probabilities to claim success at the interim or final analysis

Scenario	Look	# of patients	Simulated cumulative probabilities (%) to claim success	Simulated incremental probabilities (%) to claim success
p=0.4	Interim	30	42%	
	Final	45	78%	36%
p=0.45 (H ₁)	Interim	30	64%	
	Final	45	93%	29%
p=0.5	Interim	30	83%	
	Final	45	99%	16%

Note: Simulation is performed in R 3.0.0 with number of simulations = 10,000.

In addition, the DMC will review safety data periodically.



10.8 Sample size calculation

The final primary analysis will be performed when at least 50 acute lymphoblastic leukemia or lymphoblastic lymphoma patients (with at least 40 patients <18 years of age) have received CTL019 infusion and completed 6 months from study day 1 infusion or discontinued earlier.

The sample size calculation is primarily based on the hypothesis testing for acute lymphoblastic leukemia patients.

The number of acute lymphoblastic leukemia and lymphoblastic lymphoma patients to be treated respectively will be based on the actual recruitment of the two populations. It is anticipated that the lymphoblastic lymphoma population is small and will represent less than 10% of the entire population. Therefore with 50 patients treated in the study, it is assumed that 45 acute lymphoblastic leukemia patients will be treated.

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

Based on the null hypothesis of $ORR \leq 20\%$ and alternative hypothesis of $ORR > 20\%$, 45 acute lymphoblastic leukemia patients in the FAS will provide 93% power to demonstrate statistical significance using a 2-look Lan-Demets group sequential design with O'Brien-Fleming type boundary at one-sided 0.025 level of significance, if the underlying ORR is 45%. The actual number of patients to be enrolled will depend on the pre-infusion dropout rate. Limited data are available so far to provide robust estimate on the pre-infusion dropout rate. Assuming 20% to 25% enrolled patients will not be infused due to reasons such as product manufacturing issues, worsening of patient's condition, etc., at least 63 to 67 patients need to be enrolled respectively to ensure at least 50 infused patients (including 40 patients less than age of 18) are treated and hence will be used for the primary analysis.

10.9 Power for analysis of key secondary variables

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

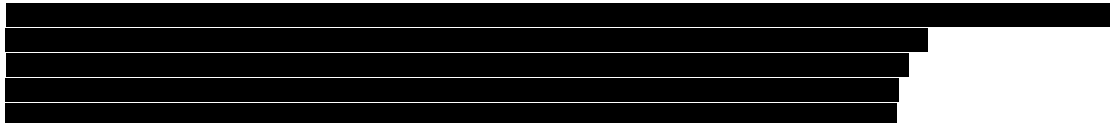
11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/SRC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Institutional Biosafety Committee/Scientific



Review Committee (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IBCs/ REBs, and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/ IEC/ REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent/assent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent/assent should be documented in the patient source documents. The date when a patient's informed consent/assent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) and assent form that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF/assent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/ IEC/ REB and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/ REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in [Section 4.3](#).

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.



11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis sponsored study, each site will permit authorized representatives of Novartis and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For eCRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Novartis 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 investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent/assent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.



11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

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

12.1 Amendments to the protocol

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



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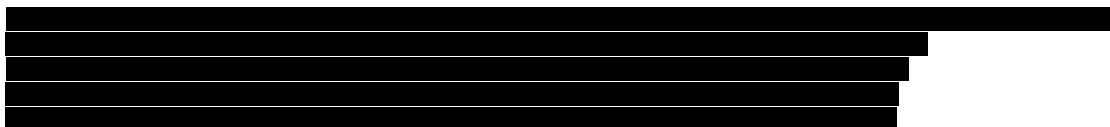
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14 Appendices

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

Author(s) [REDACTED]
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Document History

Version	Date	Changes
Final 1.0	5-Mar-2014	First version
Final 1.1	23-Dec-2014	Change the calculation of overall response date so that if the overall response classified as "No response", the date of overall response will be calculated as the earliest of any component that reveals lack of response.
Final 1.2	26-Aug-2015	<ul style="list-style-type: none">• Clarify that the qualitative assessment of tumor involvement will be used to determine response status when no blast count result is available from either bone marrow biopsy or aspirate.• Clarify that peripheral blood can be considered to be in remission status when bone marrow is in remission status at the same time.• Change the baseline disease assessment definition to indicate that the most current assessments within the protocol specified window will be used

[REDACTED]

List of abbreviations

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



14.1.1 Introduction

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

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

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

The objectives of this document are to:

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

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

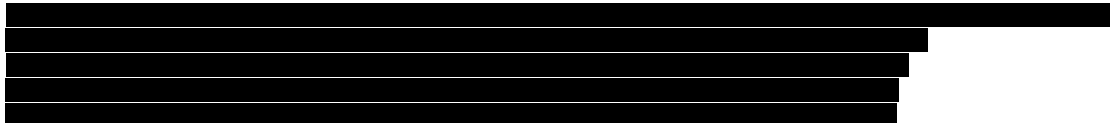
14.1.2 Efficacy evaluation

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

14.1.2.1 Types of efficacy assessments

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

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



For timing of the disease assessments for response classification, see [Section 14.1.2.3.1](#) for details. The timing of each assessment for disease response should coincide with the other response assessment timing.

14.1.2.1.1 Assessment of bone marrow blast counts

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

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

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

14.1.2.1.2 Assessment of peripheral blood

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

In some rare cases the blood results are not available (e.g. typically when WBC < 500 preventing an accurate assessment of differential count), but the bone marrow result is showing complete remission status (per definition in Table 14-1). In this case, the patient will also be considered to be in remission status in peripheral blood.

14.1.2.1.3 Assessment of extramedullary disease

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



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

14.1.2.1.3.1 Assessment of CNS disease

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

The classification of CNS status includes the following:

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

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

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

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

14.1.2.1.3.2 Assessment of mediastinal disease

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

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

14.1.2.1.3.3 Assessment of other extramedullary disease

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

Hepatomegaly and splenomegaly due to leukemic involvement, disease involvement by lymph nodes, infiltration of the skin or gums, unilateral or bilateral testicular mass, or other masses will be assessed by physical exam. Results will be coded as “Normal”, “Abnormal with no or low suspicion for leukemic involvement”, or “Abnormal with high suspicion for leukemic involvement”. The rationale for these three categories is as follows. Other



abnormalities that are not related to leukemic infiltration can often be observed in these organ sites on physical examination in patients with ALL, especially during the first 28 days after lymphodepleting chemotherapy followed by CTL019 cell infusion. Definitive proof of leukemic infiltration (e.g. liver biopsy) is often not definitive, indicated or ethically justified. Some abnormalities may occur (e.g. ecchymosis in skin or gums, acute/transient hepatosplenomegaly associated with acute infections or Macrophage Activation Syndrome (MAS)) but are clearly not leukemic involvement. Therefore three categories will more accurately capture these different clinical scenarios. In the analysis, “Normal” or “Abnormal with no or low suspicion for leukemic involvement” will be considered eligible for overall CR or CRi assessment; “Abnormal with high suspicion for leukemic involvement” will not be considered eligible for overall CR or CRi assessment, and will be considered to trigger relapsed disease assessment. Serial physical examinations for these assessments will be performed (at protocol specified frequency) to validate the persistence or resolution of such findings.

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

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

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods. Patients who experienced a CR according to morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow: up to 10^{10} malignant cells which can confer a poor outcome. The most frequently used methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and PCR assays to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes or fusion transcripts (e.g. BCR-ABL). Current flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-4} (<0.01%) 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 (RQ-PCR), sampling of bone marrow MNC is preferred. At least 1×10^7 MNCs are required for initial marker characterization and generation of individual dilution series; 1×10^6 MNCs are sufficient for follow-up analysis. The minimal limit of assay sensitivity (to declare MRD negativity) should be less than 1×10^{-4} (< 0.01%).

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



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

MRD assessment by flow cytometry or RQ-PCR should be performed via a central certified lab with 0.01% sensitivity. [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](#))
- CSF cytology via lumbar puncture for WBC, RBC cell and lymphoblast numbers ([Section 14.1.2.1.3.1](#))
- CNS imaging (CT or MRI of brain) if clinical signs of CNS leukemia exist ([Section 14.1.2.1.3.1](#))
- Physical exam for extramedullary disease ([Section 14.1.2.1.3.3](#))
- MRD assessment by flow cytometry ([Section 14.1.2.1.4](#))
- Cytogenetics and/or FISH from bone marrow aspirate

For disease characterization at baseline, the most current bone marrow assessment within the protocol specified window should be used as the baseline bone marrow assessment. The blood count and extramedullary disease (physical exam, CSF, etc) assessments that are most proximal to the above defined baseline bone marrow assessment should then be used as the baseline blood count and baseline extramedullary disease assessments, respectively.

14.1.2.3 Post-baseline overall disease response evaluation

14.1.2.3.1 Components and timing of overall disease response evaluation

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

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

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

In addition,

- Post-baseline bone marrow biopsies and/or aspirates ([Section 14.1.2.1.1](#)) for morphologic blast cell counts are required to demonstrate that a patient has achieved CR or CRi for the first time. Following initial achievement of CR or CRi, a bone marrow biopsy or aspirate will not be required unless it is clinically indicated (e.g. worsening of platelet or

[REDACTED]

neutrophils; reappearance of blast in peripheral blood, etc.) or as specified per individual protocol.

- Post-baseline CSF cytology via lumbar puncture ([Section 14.1.2.1.3.1](#)) is required to demonstrate that a patient has achieved CR or CRi for the first time. Following initial achievement of CR or CRi, a lumbar puncture will not be required unless it is clinically indicated by the presence of neurologic symptoms and as specified per individual protocol.
- MRD assessment ([Section 14.1.2.1.4](#)) should be performed per protocol specification.

In order for all components of disease assessments to be qualified as the same response evaluation, peripheral blood sample collection, CNS symptom assessment, physical exam, bone marrow biopsy/aspirate (if needed) and lumbar puncture (if needed) need to be performed, in general, within 14 days of each other, unless specified otherwise in the protocol.

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

Also see [Section 14.1.2.3.2](#) and [Section 14.1.2.3.4](#) for the definition and confirmation of disease response.

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

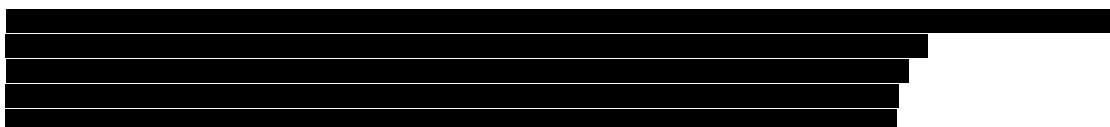
14.1.2.3.2 Response criteria

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

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

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

Response category	Definition
Complete remission (CR)	<p>All the following criteria are met:</p> <p>Bone marrow</p> <ul style="list-style-type: none"> • Trilineage Hematopoiesis (TLH) and < 5% blasts <p>Peripheral blood</p> <ul style="list-style-type: none"> • Neutrophils > 1.0 x 10⁹/L, and • Platelets > 100 x 10⁹/L, and • Circulating blasts < 1% <p>Extramedullary disease</p> <ul style="list-style-type: none"> • No clinical evidence of extramedullary disease (by physical exam and CNS symptom assessment) and • If additional assessments (e.g. CSF assessment by LP, CNS imaging, biopsy, etc.) are performed, results must show remission status <p>Transfusion independency (see Section 14.1.2.3.3).</p> <ul style="list-style-type: none"> • No platelet and/or neutrophil transfusions less than or equal to 7 days before the



Response category	Definition
	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: <ul style="list-style-type: none"> • Neutrophils $\leq 1.0 \times 10^9/L$, or • Platelets $\leq 100 \times 10^9/L$, or • Platelet and/or neutrophil transfusions less than or equal to 7 days before the date of the peripheral blood sample for disease assessment
No response	Failure to attain the criteria needed for any response categories or relapse
Relapsed Disease	Only in patients who achieved a CR or CRi and who have: <ul style="list-style-type: none"> • Reappearance of blasts in the blood ($\geq 1\%$), or • Reappearance of blasts in bone marrow ($\geq 5\%$), 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 be assessed as “relapsed disease” with the relapsed component alone.

14.1.2.3.3 Evaluation of transfusion dependency

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

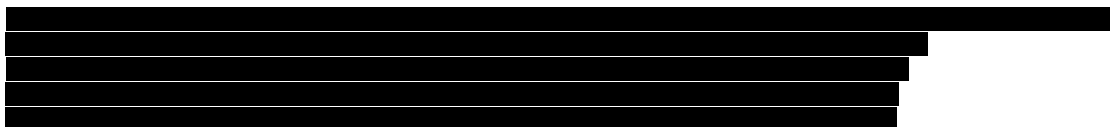
A period of at least one week (7 days) without any transfusion has been taken as a convention to define the status of transfusion independence to assess a CR vs CRi response ([Cheson et al 2006](#)). Any sample of peripheral blood sample for disease assessment which was taken less than or equal to seven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

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

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

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

Therefore, following initial achievement of CR/CRi, patients will be considered to have maintained a clinical CR/CRi if the patient has no evidence of extramedullary disease (by



physical exam and CNS symptom assessment) and circulating blasts in peripheral blood are <1%.

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

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

14.1.2.3.5 Date of overall disease response evaluation

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

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

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

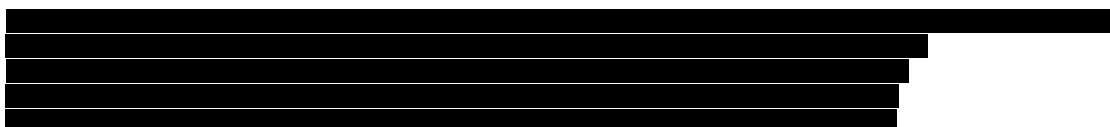
14.1.3 Data collection

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 <ul style="list-style-type: none"> ● bone marrow; ● blood; ● CNS disease; ● other extramedullary disease.
Bone marrow biopsy / aspirate	Aspirate or biopsy; morphologic blast counts and MRD assessment.
Blood response	Response status for platelets, neutrophils, morphologic blast counts; status of platelet and/or neutrophils transfusion.
CSF assessment ¹	CSF lymphoblast, WBC, RBC



(e)CRF module	Specification
Other CNS disease	CNS symptoms, confirmation of CNS disease via imaging or other methods (if applicable)
Extramedullary disease by physical exam	Presence/absence, location, method of assessment, confirmation by biopsy or imaging or not if feasible
Blood component transfusions	Type and number of units of transfusions, timing with respect to disease assessment
Hematopoietic Stem Cell Transplant (SCT) – post infusion	Date, type of post-treatment SCT

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

14.1.3.2 Recording response evaluation on the (e)CRFs

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

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

When relapse can be judge based on any component. E.g. if a relapse is observed from blood sample alone without bone marrow assessment etc. at any time, it will be recorded on the (s)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 investigator’s assessments which differ from calculated response based on the rules of this document. This discrepancy may be queried for clarification. However, the investigator’s response will not be overruled in any case.

14.1.4 Efficacy analysis definitions

14.1.4.1 Local vs central evaluation of efficacy

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

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

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



14.1.4.2 Best overall disease response

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

Best response will be assigned according to the following order:

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

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

The overall remission rate (ORR) is defined as the proportion of patients with a best overall disease response of CR or CRi.

14.1.4.3 Time-to-event definitions

General rule for the calculation of the time to event interval is:

$$\text{Time to event} = \text{event date} - \text{start date} + 1 \text{ (in days)}$$

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 SCT for the calculation of OS must be clearly specified in the protocol. See also [Section 14.1.4.4](#) for more discussion.

OS will be assessed in all patients (FAS).

14.1.4.3.2 Duration of remission (DOR)

Duration of remission (DOR) is defined as the duration from the first documented onset of CRi or CR to the date of relapse or death due to ALL.



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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy
- Event after at least two missing scheduled disease assessment

In addition, death due to reason other than ALL can be considered as either a competing risk event to other events of interest (relapse or death due to ALL), or a censoring event. The protocol should clearly specify which analysis is used as the primary analysis for DOR.

Since patients in remission might choose to receive SCT, censoring due to SCT will overestimate the risk of relapse and therefore may be considered inappropriate for the main analysis, when there is a substantial number of patients choose to receive SCT ([CHMP 2010](#)). The handling of SCT for the calculation of DOR must be clearly specified in the protocol.

See also [Section 14.1.4.4](#) for more discussion.

DOR will be assessed only in patients with the best overall response of CR or CRi.

14.1.4.3.3 Relapse-free survival (RFS)

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

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy
- Event after at least two missing scheduled disease assessment

The handling of SCT for the calculation of RFS must be clearly specified in the protocol.

See also [Section 14.1.4.4](#) for more discussion.

RFS will be assessed only in patients with the best overall response of CR or CRi.

14.1.4.3.4 Event-free survival (EFS)

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

- Death from any cause
- Relapse



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

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

In case a patient does not experience an event (e.g. discontinuation as a result of withdrawal of consent, lost to follow-up, protocol violation or administrative problems) prior to data cutoff, EFS is censored at the last adequate response assessment date on or prior to the earliest censoring event. The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy
- Event after at least two missing scheduled disease assessment

The handling of SCT for the calculation of EFS must be clearly specified in the protocol.

See also [Section 14.1.4.4](#) for more discussion.

EFS will be assessed in all patients (FAS).

14.1.4.4 Event and censoring date, sensitivity analyses

This section outlines the possible event and censoring dates for relapse ([Table 14-3](#)), addresses the issues of missing response assessments during the study, and the options for handling new anticancer therapy. It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of sensitivity analyses to be performed.

SCT is a standard treatment option for ALL patients. For time-to-event endpoints it needs to be specified in the protocol how patients who choose to undergo SCT following study protocol treatment will be handled for analysis.

Using the draft [FDA guideline \(2007\)](#) on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics) and the EMA guideline on the evaluation of Anticancer Medicinal Products in Man on Confirmatory studies in Haematological Malignancies ([CHMP 2010](#)) as references, the following analyses can be considered:

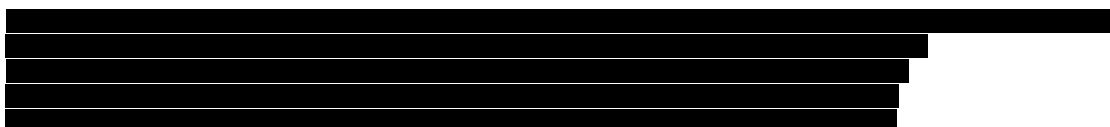


Table 14-3 Options for event dates used in DOR, EFS and RFS

Situation		Options for event date (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment	Censor
B	Relapse at scheduled assessment date or before next scheduled assessment	(1) Date of relapse (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 SCT)	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censor Censor Event Ignored
E	SCT	(1) Date of SCT (2) N/A (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 ALL (for 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.

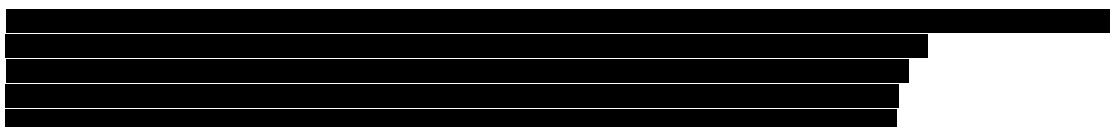
Situations C (C1 and C2): Relapse or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (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 (CIF), instead of the usual KM, is used to estimate the probability of remaining free of the event of interest in the presence of the competing risk (Kim 2007).

Situation F: Note that the KM method used to analyze DOR in the presence of censoring can be biased if the censoring event is not independent to the event of interest (i.e. relapse and death due to ALL). Therefore, analysis can also be performed considering death due to reason other than ALL as a competing risk event. In this case, the cumulative incidence function (CIF) instead of KM is used to estimate the probability of relapse in the presence of the competing risk (Kim 2007).

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-3 the “Date of last adequate assessment” by the “Date of previous scheduled assessment (from baseline)”, with the following definition:

Date of previous scheduled assessment (from baseline) is the date when a response assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate assessment.

The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and have to be specified in the study protocol or RAP documentation.

14.1.5 References

Appelbaum, FR, et al (2007) End points to establish the efficacy of new agents in the treatment of acute leukemia. *Blood* 109: 1810-1816.

Cheson B, Bennet JM, Kopecky K, et al (2003) Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *Journal of Clinical Oncology*; 21(24):4642-9.

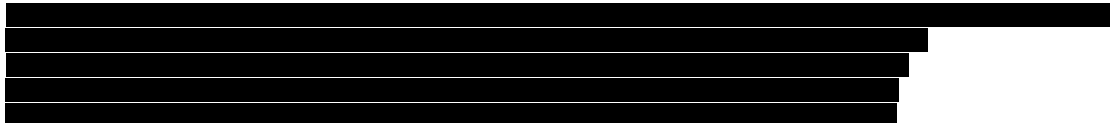
Cheson BD (2007a) The international harmonization project for response criteria in lymphoma clinical trials. *Hematol Oncol Clin N Am* 21:841-854.

Cheson BD, Pfistner B, Juweid ME, et al (2007b) Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579-586.

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updating the National Cancer Institute–Working Group 1996 guidelines. *Blood* 111.12: 5446-5456.

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Cheson BD, Greenberg P, Bennett J, et al (2006) Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*; 108: 419-425.

Kim H (2007) Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis. *Clinical Cancer Research* 2007;13:559-565.



14.2 Appendix 2: Guidelines for efficacy evaluation in Lymphoblastic Lymphoma patients

14.2.1 Introduction

The efficacy evaluation in lymphoblastic lymphoma patients follows the same guidelines for acute lymphoblastic leukemia (ALL) patients as outlined in [Appendix 1](#). In addition, based on the standardized response criteria defined by National Comprehensive Cancer Network (NCCN) Guidelines ([NCCN 2013 v1](#)) and further supported by other literatures, considerations outlined below should be followed.

14.2.2 Types of efficacy assessments

In addition to all the efficacy assessments for ALL patients, mediastinal disease must be assessed for extramedullary disease.

14.2.2.1 Assessment of mediastinal disease

A baseline CT or MRI (CT/MRI) scan of the mediastinum is only required to confirm whether mediastinal disease is present for patients with a history of lymphoblastic lymphoma. If a patient does not have a history of lymphoblastic lymphoma, no CT/MRI scan is required throughout the study.

For patients with history of lymphoblastic lymphoma, the frequency and timing of post-baseline chest CT/MRI assessment may depend upon the study setting (e.g. front line or relapse/refractory, pediatric vs adult, etc.) and should be clearly specified in the protocol. Post-baseline chest CT/MRI assessment is required at Month 1 only for patients with proven mediastinal disease at baseline. Additional chest CT/MRI assessments may be performed per protocol specification.

If at any time point, mediastinal disease is present by CT/MRI assessment, then follow-up CT/MRI is required to document the absence of mediastinal involvement whenever the patient meets all other criteria for complete remission. The timing of the CT/MRI must be within the required time window of the other disease response components.

For optimal evaluation of patients, the same imaging method of assessment (i.e. CT or MRI) and technique (i.e. with or without contrast) should be used to characterize each identified and reported lesion at baseline and during follow-up. A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without intravenous contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa).

The investigator or the central blinded reviewer should decide if a definitive overall radiological response can be provided and justified to be based on the available information. Otherwise, overall lesion response should be “Unknown”, unless there is evidence of relapse.

Although the NCCN guideline has provided some guidance on the classification of mediastinal response, the exact definition of lymph node normalization requires further clarification. Following the NCCN guideline ([NCCN 2013 v1](#)) and also referencing the



international harmonization project revised response criteria for lymphoma ([Cheson et al 2007a](#) and [Cheson et al 2007b](#)), the following guidelines are adopted:

Radiological classification of mediastinal lymph nodes

Lymph nodes in the mediastinum are classified according to their size and/or relationship to the disease:

- A lymph node that can be measured accurately in 2 perpendicular dimensions and if the long axis is > 15 mm, regardless of the length of the short axis above will constitute a **measurable nodal lesion**.
- A lymph node not meeting the measurability requirement (above) but with long axis > 15 mm (e.g. short axis cannot be measured accurately) will constitute a **non-measurable nodal lesion**
- A lymph node not meeting the measurability criteria but with a size of 11 mm to 15 mm in the long axis and > 10 mm in the short axis will be checked for relationship to disease:
- If it is thought to be disease related, it will constitute a **non-measurable nodal lesion**
- If it is not thought to be disease related, it will constitute an **abnormal lymph node** but not a lesion.
- All other lymph nodes will be considered normal and will not constitute nodal lesions.

Normalization of mediastinal lymph nodes after baseline

Mediastinal lymph nodes will be considered to have normalized if:

- A measurable nodal lesion has become ≤ 15 mm in long axis.
- A non-measurable nodal lesion has decreased to ≤ 10 mm in the short axis and be ≤ 15 mm in long axis.

New mediastinal lymph nodes

A new mediastinal lymph node is defined as:

- Either a previously normal mediastinal lymph node becoming > 15 mm in any axis, or,
- A previously identified abnormal mediastinal lymph node showing an increase of at least 50% in the long axis.

Response criteria for mediastinal disease

The response for measurable mediastinal lymph nodes is evaluated by calculating the Sum of the Products of the greatest perpendicular Diameters (SPD) of all measurable lesions (see [Table 14-4](#)), except when there is complete normalization of all measurable mediastinal lymph nodes.



Table 14-4 Response criteria for mediastinal disease

Response Status ¹	Criteria
Complete Response (CR)	Complete normalization of all mediastinal lymph nodes
CR Unconfirmed (CRu)	Residual mediastinal lymph nodes that have regressed by >75% in the SPD from baseline & without unequivocal worsening of non-measurable lymph nodes
Partial Response (PR)	At least 50% decrease from baseline in the SPD of all measurable mediastinal lymph nodes & without unequivocal worsening of non-measurable lymph nodes
No Response (NR)	Failure to attain the criteria needed for CR, CRu or PR
Relapse	Recurrence of mediastinal lymph nodes after achieving mediastinal CR or CRu

¹ At each assessment (if the measurable mediastinal lymph nodes are not in CR status), the response status based on SPD calculation will be first assessed for meeting NR status criteria, then PR status.

Note that NCCN guidance has defined a mediastinal progressive disease (PD) category. In this document, mediastinal PD is considered the same as “No response”. The difference between mediastinal progressive disease and no response in lymphoblastic lymphoma within the mediastinum is not believed to be clinical meaningful.

14.2.2.2 Baseline Evaluation

CT or MRI scan is required for patients with a history of lymphoblastic lymphoma.

For disease characterization at baseline, the most current bone marrow assessment within the protocol specified window should be used as the baseline bone marrow assessment. The blood count and extramedullary disease (physical exam, CSF, imaging if indicated) assessments that are most proximal to the above defined baseline bone marrow assessment should then be used as the baseline mediastinal disease assessments.

14.2.2.3 Post-baseline overall disease response evaluation

Post-baseline CT/MRI for mediastinal disease assessment is required to demonstrate that a patient has achieved CR or CRi for the first time. IN order for all components of disease assessments to be qualified as the same response evaluation, peripheral blood sample collection, CNS symptom assessment, physical exam, bone marrow biopsy/ aspirate (if needed), CT/MRI scan (if needed) and lumbar puncture (if needed) need to be performed, in general, within 14 days of each other, unless specified otherwise in the protocol.

The overall disease response is determined at a given evaluation using the criteria described in [Table 14-5](#) below.

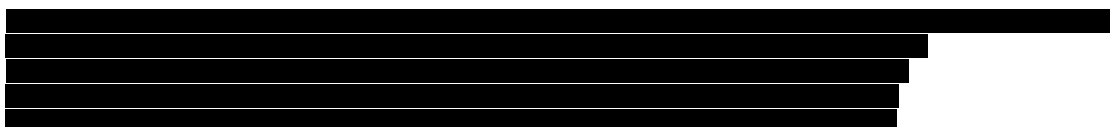


Table 14-5 Overall disease response classification at a given evaluation time for lymphoblastic lymphoma patients

Response category	Definition
Complete remission (CR)	All the criteria for ALL are met, and in addition CR for mediastinal disease.
Complete remission with incomplete blood count recovery (CRi)	All the criteria for ALL are met, and in addition CR for mediastinal disease.
CR or CRi with residual mediastinal disease	All criteria for CR or CRi as defined above are met, except that mediastinal disease as defined by CRu or PR is observed.
No response	Failure to attain the criteria needed for any response categories or relapse
Relapsed Disease	Same criteria for ALL, and in addition mediastinal relapse will also indicate relapse for lymphoblastic lymphoma.
Unknown	Same criteria for ALL.

Note that the NCCN guideline ([NCCN 2013 v1](#)) has defined mediastinal response criteria including CRu and PR, however has not incorporated these categories into the overall disease response. Residual nodal disease in the presence of clearance of all other sites of disease may represent a unique biologic setting. Therefore, in the case a patient achieves CR or CRi at all other non-mediastinal disease sites, and has residual mediastinal disease (mediastinal CRu or PR), a category for overall disease response of “CR or CRi with residual mediastinal disease” has been included in this document, which is not part of the NCCN guideline. The clinical significance of such a category, however, has not been demonstrated.

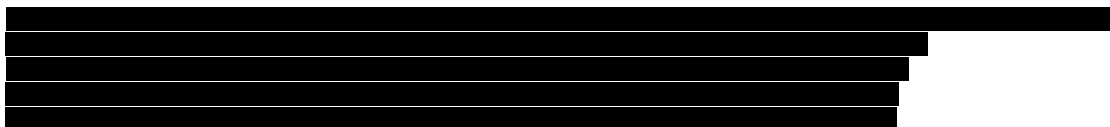
14.2.2.3.1 Establishing and subsequent maintenance of response with no clinical evidence of relapse

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

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

14.2.2.3.2 Date of overall disease response evaluation

Dates of CT/MRI scans are also considered in the same fashion as other components to determine the date of overall response for lymphoblastic lymphoma patients.



14.3 Appendix 3: Eligibility based on serologic markers for hepatitis B infection

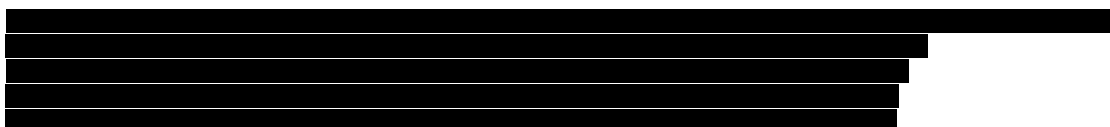
Test	Results				
HBsAg	+	-	-	-	-
Anti-HBc	Any	+	-	+	-
Anti-HBs	Any	-	+	+	-
Eligibility	Not Eligible	Not Eligible	Eligible	Eligible	Eligible

If indeterminate results are obtained, viral DNA levels should be measured to confirm negative viral status.

HBsAg positive: Indicates active infection and/or chronic active and potential for reactivation with fulminant hepatitis. These patients are not eligible for this trial.

Anti-HBs positive: Protective – Indicates vaccination or previous infection that has been successfully resolved. These patients are eligible for this trial.

HBsAg negative, Anti-HBc positive, Anti-HBs negative: Indicates latent infection. These patients are also at risk for viral reactivation. These patients are not eligible for this trial.



14.4 Appendix 4: CTL019 Modified Safety Reporting

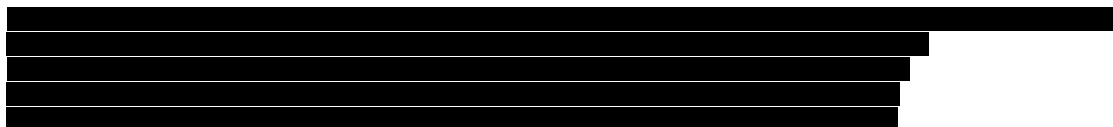
14.4.1 Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	Post-treatment Period (Starting from LD chemo/pre-infusion visit)	
		Through Month 12 Visit	After Month 12 Visit, through Month 60
Non-serious Adverse Events (AE)	Modified: <ul style="list-style-type: none"> • All infections • All laboratory abnormalities deemed clinically significant by the investigator • All clinical AEs grade ≥ 3 • All AEs related to a study procedure • All AEs leading to study discontinuation 	All, including all laboratory abnormalities deemed clinically significant by the investigator	Modified –Whether serious or non-serious, report following: <ul style="list-style-type: none"> • Events leading to death • Related to a study procedure • Infections <ul style="list-style-type: none"> • Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria: Require anti-infective treatment OR Lead to significant disability or hospitalization OR Need surgical or other intervention • New incidence or exacerbation of a pre-existing neurologic disorder • New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder • New incidence of other hematologic disorder • Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy • Positive RCL test result • Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene • New malignancy (T-cell & non T-cell), other than the primary malignancy • Progressive multifocal leucoencephalopathy (PML) • Hepatitis B reactivation
Serious Adverse Events (SAE)	Modified: <ul style="list-style-type: none"> • All events leading to death • All events related to a study procedure • Any AE reportable for this study period that also meets criteria for serious • All pulmonary or cardiac abnormalities • All infections • Any substantial change in the status of the patient that precludes the patient from proceeding to study treatment (e.g. GVHD, rapid progression of malignancy, marked decline in performance status) • Any other substantial change in the status of the patient that the investigator deems may have a potential impact on the patients during lymphodepletion and CTL019 treatment 	All	



14.4.2 Concomitant Medication

	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	Post-treatment Period (Starting from LD chemo/pre-infusion visit, through Month 12)		Post-treatment Period (After Month 12, through Month 60)
	Inpatient/ICU OR Outpatient	Inpatient/ICU	Outpatient	Inpatient/ICU OR Outpatient
Concomitant medications	<p>Modified:</p> <p>Drugs: Record all of the following medications:</p> <ul style="list-style-type: none"> ● Anticytokine therapies (e.g. tocilizumab, or other) ● Corticosteroids (including prophylactically for blood product administrations, physiologic replacement doses, high or stress doses, etc.) ● Anti-seizure medications ● Allopurinol, or non-allopurinol alternatives ● Rasburicase ● Immunoglobulin therapy ● Any medication given therapeutically for an SAE ● Vasopressors and cardiac inotropic agents (see below) ● Narcotics and sedatives (see below) ● Antineoplastic therapies (e.g. lymphodepleting chemotherapy) ● Related to an AE or SAE defined as reportable for this period <p>Vasopressors and cardiac inotropic agents:</p> <ul style="list-style-type: none"> ● For dose, record only maximum daily rate (e.g. ug/kg/hr, mg/hr, etc.) <p>Narcotics and sedatives:</p> <ul style="list-style-type: none"> ● For dose, record only total daily dose <p>Blood products (e.g. red cells, platelets, FFP, cryoprecipitate):</p> <ul style="list-style-type: none"> ● If administered ≤7 days of a tumor response assessment: ● Record ALL blood products, including prophylaxis (to distinguish CR vs CRi) ● If NOT administered ≤7 days of a tumor response assessment: ● Only record blood products if given for bleeding (excludes prophylactic use) <p>Electrolyte & vitamin replacement:</p> <ul style="list-style-type: none"> ● Record all electrolyte replacement if given for a ≥ Grade 3 electrolyte disturbance and list these as an adverse event (AE). ● Do <u>not</u> record ≤ Grade 2 or prophylactic use of electrolyte or vitamin replacements ● Do <u>not</u> record total parenteral nutrition (TPN) on concomitant medication CRF <p>Fluids:</p> <ul style="list-style-type: none"> ● Do <u>not</u> record fluid boluses and maintenance fluids 		All	<p>Modified:</p> <ul style="list-style-type: none"> ● Related to an AE or SAE defined as reportable for this period ● Mutagenic agents (including cytotoxic drugs) ● Radiation & antineoplastic therapy (including SCT) ● Immunoglobulin therapy ● Immunosuppressive agents (including dose of steroids higher than physiologic replacement therapy doses of steroids (6-12 mg/m2/day hydrocortisone or equivalent)) ● Investigational therapy



	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	Post-treatment Period (Starting from LD chemo/pre-infusion visit, through Month 12)		Post-treatment Period (After Month 12, through Month 60)
	Inpatient/ICU OR Outpatient	Inpatient/ICU	Outpatient	Inpatient/ICU OR Outpatient
Laboratory data	<p>Modified:</p> <ul style="list-style-type: none"> Record <u>all</u> scheduled labs (per Visit Evaluation Schedule) Record <u>all</u> results (scheduled or unscheduled) for: LDH, Uric acid, [REDACTED], and fibrinogen (related to CRS/TLS/MAS) Record all other laboratory values if they are ≥ Grade 3 For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled) <ul style="list-style-type: none"> For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia) Laboratory abnormalities that are treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding) 		All	<p>Modified:</p> <ul style="list-style-type: none"> Record <u>all</u> scheduled labs (per Visit Evaluation Schedule) Record <u>all</u> results (scheduled or unscheduled) for: LDH, Uric acid, [REDACTED] and fibrinogen (related to CRS/TLS/MAS) Record all other laboratory values if they are ≥ Grade 3 For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled) <ul style="list-style-type: none"> For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia) Laboratory abnormalities that are treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)

[REDACTED]