CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)
Protocol Number:	KTE-C19-103 (ZUMA-3)
Kite Investigational Product:	KTE-X19
USAN:	Brexucabtagene Autoleucel
IND Number:	016675
EudraCT Number:	2015-005009-35
ClinicalTrials.gov Identifier:	NCT02614066
Clinical Study Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Key Sponsor Contacts:	The medical monitor name and contact information is included on the Study Contact Lists distributed by the CRO.
Protocol Version/Date:	Original: 07 May 2015 Amendment 7: 14 December 2021

SPONSOR AND INVESTIGATOR SIGNATURE PAGE

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STUDY ACKNOWLEDGEMENT

A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)

Amendment 7.0, 14 December 2021

This protocol has been approved by Kite Pharma, Inc. The following signature documents this approval.

PPD

Kite Medical Monitor Name (Printed)

PPD

Sig

PPD

Date

INVESTIGATOR STATEMENT

I have read the attached protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete this study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner and dependent children)
- Sub-Investigators (including, if applicable their spouse, legal partner and dependent children) at the start of the study and for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma Inc.

Principal Investigator Name (Printed)

Signature

Date

Site Number

STUDY GLOSSARY

AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CAR	chimeric antigen receptor
CAR+	chimeric antigen receptor positive
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CPF	cell processing facility
CR	complete remission
CRh	complete remission response with partial hematologic recovery
CRi	complete remission response with incomplete hematologic recovery
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
ddPCR	droplet digital polymerase chain reaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of remission
DSMB	data safety monitoring board
DVT	deep vein thrombosis
eACT™	engineered autologous cell therapy
ECHO	echocardiogram
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	electroencephalogram
End of Study for individual subject	Defined as when the last day that protocol specified assessments are conducted for an individual subject
End of Study (primary completion)	Defined as when the last subject is assessed or received an intervention for the purposes of final collection of data for the primary endpoint at Week 8
End of Study (end of trial)	Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments
High Burden Disease	M3 marrow (>25% leukemic blasts) or ≥ 1000 blasts/mm^3 in the peripheral circulation
HLH	Hemophagocytic lymphohistiocytosis
ICF	informed consent form
IHC	immunohistochemistry

IL	interleukin
IL-2R	interleukin-2 receptor
IP	investigational product
IPM	Investigational product manual
IRB/IEC	institutional review board/independent ethics committee
KTE-X19	autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3-zeta chimeric antigen receptor
LMWH	low-molecular weight heparin
LTFU	long term follow-up
LVEF	left ventricular ejection fraction
mITT	modified intend to treat
MTD	maximum tolerated dose
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
OS	overall survival
PBMC	peripheral blood mononuclear cells
PET	positron emission tomography
Ph^+	Philadelphia chromosome positive
PMBCL	primary mediastinal B-cell lymphoma
PD	progressive disease
PR	partial response
qPCR	quantitative polymerase chain reaction
RCR	replication competent retrovirus
RFS	relapse-free survival
r/r	relapsed/refractory
SAE	serious adverse event
scFv	single chain variable fragment
SMZL	splenic marginal zone lymphoma
SOA	schedule of assessments
SOC	standard of care
SCT	stem cell transplant
Study day 0	Defined as the first day that KTE-X19 is administered to the subject
TEAEs	treatment-emergent adverse events
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
ULN	upper limit normal
WBC	white blood cell

PROTOCOL SYNOPSIS

Title:	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)
Indication:	The indication is for the treatment of adult subjects with B-precursor r/r ALL**.**
Study Design:	ZUMA-3 is a Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with relapsed or refractory B-precursor ALL. In this study, relapsed or refractory is defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogenic SCT (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment). **Phase 1 Study** During Phase 1, approximately 3-12 subjects with high burden [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for DLT will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and make recommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19. Up to approximately 40 additional subjects with high or low burden disease may be enrolled to further assess safety (see Figure 1, Section 3.1 and Section 9.6). **Phase 2 Study** During Phase 2, approximately 50 subjects in the modified-intention to treat (mITT) set will be assessed to evaluate the efficacy and safety of KTE-X19. An independent Data Safety Monitoring Board (DSMB) will review safety data through one interim analysis during the Phase 2 portion of the study. In this interim analysis, the DSMB will review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion. Each subject will provide consent and be evaluated for study participation. Once deemed eligible and enrolled into the study, each subject will follow the same study treatment schedule and procedural requirements, independent of the phase of the study, and proceed through the following study periods:

	• Screening period • Enrollment/Leukapheresis period • Bridging chemotherapy and cerebrospinal fluid (CSF) prophylaxis period • Conditioning chemotherapy period • Investigational Product (IP) treatment period • Post treatment assessment period • Long term follow-up period For study requirements assigned to each study period, refer to the schedule of assessments and Section 7 for details.
Study Objectives:	**Phase 1 Study** The primary objective of Phase 1 is to evaluate the safety of KTE-X19. **Phase 2 Study** The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission rate defined as complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) in adult subjects with r/r ALL (Appendix 1). Secondary objectives will include assessing the safety and tolerability of KTE-X19 and additional efficacy endpoints.
Hypothesis:	This study is designed to differentiate between a treatment that has a true overall complete remission rate of 40% or less and a treatment with a true overall complete remission rate of 65% or more. The hypothesis is that the overall complete remission rate to KTE-X19 is significantly greater than 40%.
Primary Endpoints:	• Phase 1: Incidence of adverse events (AEs) defined as dose-limiting toxicities (DLTs) in the DLT evaluable set • Phase 2: Overall complete remission rate (CR + CRi) per independent review (Appendix 1)
Secondary Endpoints:	• Overall complete remission rate (CR + CRi) per investigator assessment (Appendix 1) • Duration of Remission (DOR) • Minimal Residual Disease (MRD) negative rate • Allogeneic stem cell transplant (Allogeneic SCT) rate • Overall survival (OS) • Relapse-free Survival (RFS)

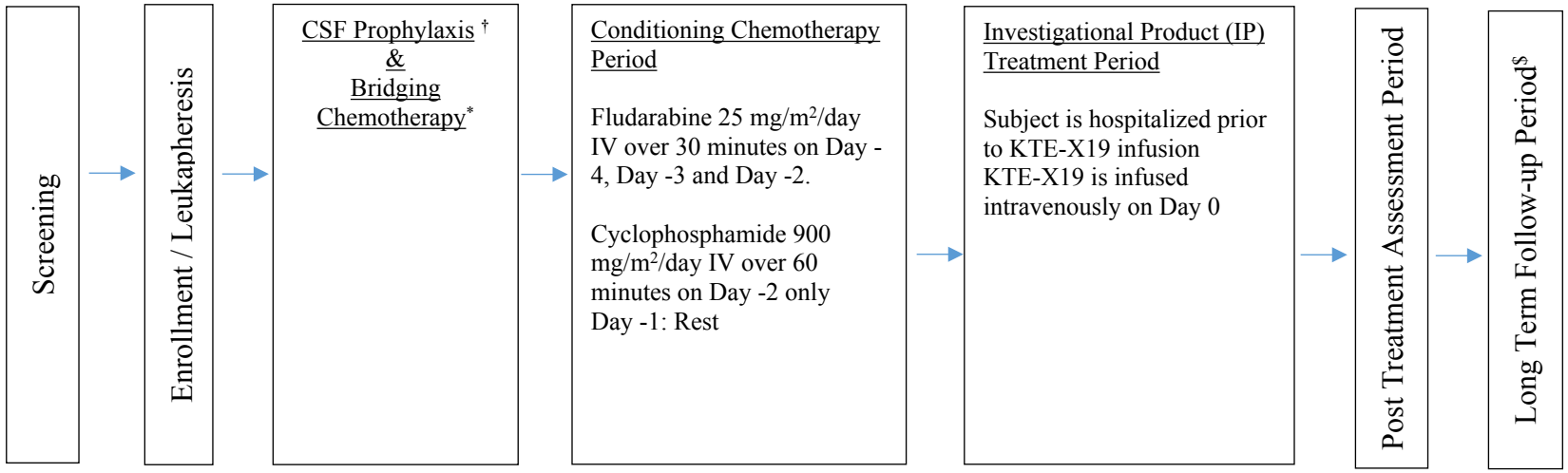
	• Incidence of AEs and common terminology criteria for adverse events (CTCAE) grade changes in safety laboratory values • Incidence of anti-KTE-X19 antibodies • Changes over time in the EQ-5D score and VAS score (phase 2 only) CCI [redacted]
Sample Size	In total, up to approximately 100 subjects may be enrolled and treated with KTE-X19 in the study in Phase 1 and 2 combined (see Sections 9.6 and 10.3). • Phase 1: Approximately 3-12 subjects evaluable for DLT and up to approximately 40 additional subjects • Phase 2: Approximately 50 subjects in the mITT set
Study Eligibility	Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both phases of the study.
Treatment	Bridging chemotherapy: • Bridging chemotherapy is recommended for all subjects particularly for those subjects with high disease burden at screening [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] • If prescribed, bridging chemotherapy must be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy. • Allowed bridging chemotherapy regimens are listed in Section 6.3, Table 2. Doses listed are recommended and can be adjusted for age/comorbidities or per local or institutional guidelines. • Refer to Sections 6.3 and 7.11.4 for further details.

	CSF Prophylaxis: • All subjects will receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose). • CSF prophylaxis will be administered any time during screening (eg, at time of screening lumbar puncture) through 7 days prior to KTE-X19 infusion. • Subjects who are enrolled with CNS-2 disease at baseline must receive CSF prophylaxis after leukapheresis and at least 7 days prior to KTE-X19 infusion, unless otherwise approved by the Kite Medical Monitor. • Multiple doses of CSF prophylaxis can be given per investigator discretion in accordance with institutional guidelines, but at least 7 days must pass between the last dose of CSF prophylaxis and KTE-X19 infusion. • Additional CSF prophylaxis may be given post-KTE-X19 infusion per investigator discretion in accordance with institutional guidelines, but should be avoided for at least 8 weeks after KTE-X19 infusion if possible. • Refer to Sections 6.4 and 7.11.5 for further details. Conditioning Chemotherapy: • All subjects will receive conditioning chemotherapy consisting of fludarabine and cyclophosphamide. • Fludarabine will be given at a dose of 25 mg/m^2/day intravenously (IV) over 30 minutes on Day-4, Day -3, and Day 2 prior to KTE-X19 infusion. • Cyclophosphamide will be given at a dose of 900 mg/m^2/day IV over 60 minutes on Day -2 prior to KTE-X19 infusion. • Refer to Sections 6.5 and 7.11.6 for further details. Investigational Product: • The day of KTE-X19 infusion is considered Day 0. • KTE-X19 infusion will be administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg, 1 x 10^6 anti-CD19 CAR T cells/kg, or 0.5 x 10^6 anti-CD19 CAR T cells/kg (see Figure 1, Section 3.1 and Section 9.6). • All subjects will be hospitalized to receive KTE-X19 infusion followed by a minimum 7 day observation period unless otherwise required by country regulatory agencies (refer to Appendix 3 for details). • Refer to Sections 6.6 and 7.11.7 for further details.

Procedures	At specific time points as outlined in the schedule of assessments, subjects will undergo the following procedures: • Collection of informed consent, general medical history including previous treatments for ALL, physical exam including height and weight, vital signs, ECOG performance status, and neurological assessments. • Lumbar punctures for collection of cerebral spinal fluid (CSF). • Bone marrow biopsies/aspirates. • If applicable, imaging modality appropriate for the anatomical site and clinical scenario (eg, positron emission tomography [PET], magnetic resonance imaging [MRI] for central nervous system [CNS] lesion, ultrasound for testicular lesion, computed tomography [CT] for intra-abdominal or thoracic lesions), will be performed to assess extramedullary disease status. • Blood will be drawn and assessed locally for complete blood count (CBC) with differential, chemistry panels, C-reactive protein, and CD3 count. CD19 expression will be assessed locally in subjects with prior blinatumomab treatment by flow cytometry or immunohistochemistry (IHC) on blasts obtained from peripheral blood or bone marrow. • Women of child-bearing potential will undergo a urine or serum pregnancy test. • Blood will be drawn and submitted to the central lab for: cytokines, lymphocyte subsets, anti-KTE-X19 antibodies, replication competent retrovirus (RCR) and anti-CD19 CAR T cell analysis. • Subjects will also undergo a baseline electrocardiogram (ECG) and echocardiogram (ECHO) • Leukapheresis. • Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events. • Subjects in phase 2 will complete the EQ-5D questionnaire.
Safety Review Team and Data Safety Monitoring Board	During Phase 1, approximately 3-12 subjects with high burden [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for DLT will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and make recommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall

	safety profile of KTE-X19. Up to approximately 40 additional subjects with high or low burden disease may be enrolled to further assess safety (see Figure 1, Section 3.1 and Section 9.6). During Phase 2, approximately 50 subjects in the modified-intention to treat (mITT) set will be assessed to evaluate the efficacy and safety of KTE-X19. An independent Data Safety Monitoring Board (DSMB) will review safety data through one interim analysis during the Phase 2 portion of the study. In this interim analysis, the DSMB will review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion.
Statistical Considerations	The primary endpoint for the Phase 2 study is the overall complete remission rate (CR and CRi) per independent review (Appendix 1). This endpoint will be based on a mITT population consisting of all Phase 2 subjects who receive KTE-X19 dose (see Section 10.5). This study uses a single-arm design to test for an improvement in overall complete remission rate. For the test of efficacy this study has approximately 93% power to distinguish between an active therapy with a 65% true overall complete remission rate from a therapy with an overall complete remission rate of 40% or less with a 1-sided alpha level of 0.025. During Phase 1, the SRT will review safety data after 3 subjects in the DLT evaluable set (see Section 10.5) have had the opportunity to be followed for 28 days after the KTE-X19 infusion (see Section 9.6). During Phase 2, one interim and one primary analysis will be performed. The interim analysis is for safety only and will be performed by the DSMB after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion. Additional interim analyses for safety may be requested by the DSMB. The primary analysis will occur when the overall study enrollment is complete and the last treated subject in the mITT set has had the opportunity to complete the month 6 disease assessment. A secondary endpoint, MRD-negative rate, will be tested against an MRD-negative rate of 30% if the testing of the primary endpoint is significant.

Study Schema



† CSF Prophylaxis (administered any time during screening through 7 days prior to KTE-X19 infusion):
All subjects will receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines must be administered. CSF prophylaxis may be administered with the screening lumbar puncture. See Section 6.4 for additional details.

* Bridging Chemotherapy (administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy)
Bridging chemotherapy is recommended for all subjects particularly those subjects with high disease burden at screening [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation]. See Section 6.3 for details.

$ After completion of the Month 24 visit, subjects who received an infusion of KTE-X19 will complete the remainder of the 15-year follow-up assessments in a separate long-term follow-up study, KT-US-982-5968.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

1. OBJECTIVES

The primary objective of Phase 1 is to evaluate the safety of KTE-X19.

The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission rate defined as complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL). Secondary objectives will include assessing the safety and tolerability of KTE-X19, additional efficacy endpoints, and change in EQ-5D scores.

2. DISEASE BACKGROUND AND RATIONALE

2.1. Overview of ALL and Epidemiology

Acute lymphoblastic leukemia is a heterogeneous group of lymphoid disorders that results from the clonal proliferation of immature lymphocytes of B-cell or T-cell lineage in the blood, bone marrow, and other organs. The disease occurs with a bimodal age distribution, with 60% of cases diagnosed in patients less than 20 years old, and 25% of cases diagnosed at age 45 years or greater. In the United States there are approximately 6,000 new ALL cases diagnosed per year, of which 2,500 are in adults. While 5-year survival rates are 80-90% in children, less than 25% of adults achieve long-term survival, and the majority of the 1,400 ALL deaths per year in the United States are in adults {National Comprehensive Cancer Network 2014, Siegel 2014}. While initial CR rates in adults are high (80-90%) and the median duration of first remission in most studies is 18 months or longer, most patients eventually experience relapse {Kantarjian 2004, Kantarjian 1994, Larson 1995, Rowe 2005}. Outcomes in the second-line and beyond setting with chemotherapy are poor with CR rates of approximately 20-40%, being lower in patients with relapse within 12 months of initial response, and overall survival (OS) being approximately 6 months, making the relapsed/refractory setting the area of greatest unmet need in ALL {Faderl 2011, Fielding 2007, Kantarjian 2003, O'Brien 2013, Tavernier 2007, Thomas 1999}.

2.2. Diagnosis and Subtyping of ALL

Diagnosis of ALL requires at least 20% lymphoblasts in the bone marrow {Harris 1999}. ALL is then further classified into 1 of 3 major subtypes by immunophenotyping: B-precursor ALL (70%), mature B-cell ALL (Burkitt lymphoma; 5%), and T-cell ALL (25%). B-cell ALLs are generally $CD10^+$, $CD19^+$, and $CD79a^+$, although precursor B-cell ALLs may be $CD10^-$. Mature B-cell ALLs additionally express surface immunoglobulin (Ig). T-cell ALLs express T-cell markers such as CD3, CD4, and CD8. The 3 immunophenotypic subtypes are associated with non-overlapping prognoses and treatments making the classification clinically relevant {National Comprehensive Cancer Network 2014}. B-precursor ALL comprises the majority of all adult ALL cases.

2.3. Philadelphia Positive vs. Negative ALL

Approximately 20-30% of adults and a small percentage of children with ALL are Philadelphia chromosome positive (Ph^+), and the majority of Ph^+ cases are of B-cell lineage {Lee 2011}. Ph^+ status confers poor prognosis, with a 5-year event-free survival (EFS) rate of 36% vs 16% and an OS rate of 41% vs. 22% in Philadelphia chromosome negative (Ph-) vs. Ph+ patients {Moorman 2007}. Ph+ status also allows for additional treatment with Abl tyrosine kinase inhibitors (TKIs) such as imatinib or dasatinib.

2.4. Treatment and Prognosis

Several anti-neoplastic agents are given in varying doses and schedules based on regional preferences and patient tolerability in 3 distinct phases for 1st line treatment: induction, intensified consolidation, and maintenance. Central nervous system (CNS) prophylaxis

accompanies induction and consolidation. The goals of treatment are to reconstitute normal hematopoiesis, prevent emergence of resistant subclones, eliminate minimal residual disease, and provide prophylaxis to sanctuary sites. Stem cell transplant also plays a role in the management of ALL, and tyrosine kinase inhibitors are added to chemotherapy and transplant regimens in patients with Ph^+ disease.

2.4.1. First-line Treatment

Most first-line regimens are a variation of either the Berlin-Frankfurt-Münster/Children's Oncology Group (BFM/COG) regimens, which include a combination of vincristine, an anthracycline, a corticosteroid, and L-asparaginase, or the Cancer and Leukemia Group B (CALGB) regimens, which include the 4 drug classes above plus cyclophosphamide {Larson 1995, Rowe 2005}. A TKI such as imatinib is included in the treatment regimen for patients with Ph^+ disease. Dexamethasone appears to decrease the risk of CNS relapse and improve EFS compared to prednisone, but at the risk of increased toxicity and no OS advantage {Mitchell 2005, Pui 2006}. The hyper-CVAD regimen which has demonstrated efficacy in ALL is a variation on the CALGB regimen with alternating regimens of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone with high-dose methotrexate and cytarabine {Kantarjian 2004}. First-line regimens yield CR rates of 80-90% in adults. Despite the high CR rates and a median duration of first remission of at least 18 months, most patients eventually relapse.

2.4.2. Second-line and Beyond Treatment

The salvage setting represents the area of greatest need in adult ALL given the poor outcomes achieved with chemotherapy in adults who have relapsed or refractory ALL. Second-line chemotherapy yields remissions in about 20-40% of patients, with the remission rate being lower in patients who relapse within 12 months of an initial response (Table 1).

In the third line and beyond setting, complete remissions with chemotherapy are seen in at most 20% of patients, and the majority of remissions are short lived {Faderl 2011, Fielding 2007, Kantarjian 2003, O'Brien 2013, Tavernier 2007, Thomas 1999}. Although long-term disease free survival (DFS) rates of autologous stem cell transplantation (ASCT) are superior to chemotherapy in the salvage setting (approximately 40% vs 20%), only 30-40% of patients who achieve a second CR are eligible for SCT, and fewer than half of the patients who achieve a second CR have enough time prior to relapse to make it to transplant {Herzig 1987, Kolb 2009, Terwey 2009}, with rates as low as 5% in adults being reported in some series {Thomas 1999}.

In December 2014, the bispecific CD19-directed CD3 T-cell engaging agent blinatumomab was granted accelerated approval in the US for the treatment of Ph^- relapsed or refractory B-cell precursor ALL {BLINCYTO 2017}. The approval was granted based primarily on findings from a single-arm study of 185 evaluable patients with r/r B-precursor ALL (relapsed with first remission duration of ≤12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of SCT). CR was achieved in 32% of patients, and an additional 9% had CRh. The majority of responses (81%) occurred within cycle 1 of treatment, 75% of those with CR/CRh had an minimum residual disease (MRD)-negative response, and the SCT rate among those who achieved CR/CRh was 39%. Duration of response/relapse-free survival in patients who had CR/CRh was 5.9 months. Results from a second study of blinatumomab, a Phase 3 trial which randomized adults with r/r ALL 2:1 to blinatumomab

versus 1 of 4 standard of care (SOC) chemotherapy regiments, have also recently been reported. A total of 405 patients were randomized, and a prespecified interim analysis occurred after 248 deaths. Median OS was 7.8 months (95% CI: 5.7, 10.0) for blinatumomab and 4.0 months (95% CI: 2.9, 5.4) for SOC (p=.011; hazard ratio=0.71), surpassing the prespecified boundary p value of 0.0183. Based on these results, this study was terminated early upon the recommendation of the study's Data Safety Monitoring Board {Topp 2016}. No studies have yet reported the outcomes of patients in the post-blinatumomab setting.

Table 1 below summarizes representative data in the salvage setting for adult ALL. Given the promising early data for chimeric antigen receptor (CAR) T-cell therapy in r/r ALL (see Section 2.6), this trial evaluates KTE-X19 in this difficult setting.

Table 1. Complete Response (CR) Rate in Adult B-Precursor Acute Lymphoblastic Leukemia (B-ALL) in the Relapsed/Refractory Setting

Trial/Reference	Treatment	Criteria	N	CR rate
Second line chemotherapy (relapsed or refractory after initial therapy for de novo disease)				
Thomas Cancer 1999	Various chemotherapy or SCT regimens	Primary refractory (24%) or primary relapsed (76%) disease	314	31% overall • 22% for patients with 1st CR of duration 1-11.9 months (n=146) • 41% for patients with first CR of duration >12 months (n=93) • 20% for Ph^+ (n=55) • 34% for primary refractory (n=75)
Tavernier Leukemia 2007	Various systemic or SCT regimens	Relapsed or refractory after initial therapy, Ph^- Relapsed or refractory after initial therapy, Ph^+	340 81	46% 37%
Welborn Am J Hema 1994	Various chemotherapy regimens	Relapsed or refractory ALL (primarily second line patients)	609	34%
Faderl Clin Lymphoma Myeloma Leuk 2011	hCVAD	Refractory (11%) or relapsed (89%; 76% of all patients in 1st relapse)	90	46% (median CR1 of responders = 16 months)
Third line or beyond chemotherapy				
Kantarjian Blood 2003	Clofarabine	2nd or subsequent salvage	8	13%
Advani Br J Haematol 2010	Clofarabine+ cytarabine	Patients in ≥ 2nd relapse	16	19% (CR/CRi)[A]
O'Brien JCO 2013	Liposomal vincristine sulfate	Ph^- ALL in 2nd or greater relapse	65	20% (CR/CRi)[A]
Novel targeted agents				
Blinatumomab USPI	Blinatumomab	Relapsed/refractory B-precursor ALL	185	• 32% CR • 9% CRh[B]
Kantarjian NEJM 2016	Anti-CD22-calecheamicin (inotuzumab oogamicin)	Relapsed and refractory ALL	49 (46 adults)	• 36% CR • 45%CRi[A] • OS HR 0.77 (97.5% CI, 0.58-1.03) inotuzumab vs. chemotherapy

A Complete remission with incomplete hematologic recovery (CRi)
B Complete remission with partial hematologic recovery (CRh)
C Complete marrow response (CMR)

2.4.3. Minimal Residual Disease (MRD)

Several studies have shown that the achievement of a minimum residual disease (MRD)-negative response (<0.01% lymphoblasts in the bone marrow) with ALL treatment is associated with prolonged leukemia remission in both pediatric and adult ALL patients {Campana 2010, Cazzaniga 2011}. However, not all subjects who achieve a morphological complete remission achieve a MRD-negative remission. In a large study by the Children's Oncology Group randomizing patients to different induction and maintenance regimens, 1788 of 2422 (74%) of subjects who had a remission (<10% bone marrow blasts) achieved MRD-negative status {Borowitz 2015}. Treatment with the bispecific T cell engager blinatumomab produces a similar proportion of MRD-negative responses, 8 of 14 (53%) pediatric patients with a CR had an MRD-negative response {von Stackelberg 2016}. Minimum residual disease-negative rates are similar in adults. With blinatumomab, 60 of 73 (82%) adult patients who achieved a CR or CRh had an MRD-negative response.

2.5. Study Rationale

Most advanced cancers eventually become refractory to conventional therapies and new treatment modalities are needed. Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and tumor infiltrating lymphocytes have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumor, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. Engineered T cells are a promising approach for cancer therapy {Kershaw 2013}.

Engineered Autologous Cell Therapy (eACT™) is a process by which a patient's own T cells are collected and subsequently genetically altered to recognize and target antigens expressed on the cell surface of specific malignancies {Kochenderfer 2013}. The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies {Davila 2014, Lee 2015, Maude 2014} and has opened possibilities for the treatment of patients with a wide variety of cancer types including B-cell malignancies expressing the CD19 antigen.

Given the poor outcomes which have been achieved to date in adults with r/r ALL (Table 1), this trial will enroll adult subjects with r/r B-precursor ALL as evidenced by failure to achieve or maintain a response to prior systemic therapy, or by recurrence after allogeneic SCT. Patients with T-cell lineage ALL will not be enrolled since their malignancies are $CD19^-$ and will likely not respond to a CD19 directed agent.

2.5.1. CD19 and Expression

CD19 is a 95 kD transmembrane protein expressed only in the B-cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B-cell malignancies including all subtypes of B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and non T-cell acute lymphoblastic leukemia (ALL) {Blanc 2011} with the exception of multiple myeloma.

2.5.2. Anti-CD19 CAR T-cell Product

Anti-CD19 CAR T cells are autologous human T cells that have been engineered to express an extracellular single chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ molecules arranged in tandem. KTE-X19 is an anti-CD19 CAR T cell product being developed by Kite Pharma under ZUMA-3.

CCI

The CAR vector construct utilized in KTE-X19 is identical to the one used in National Cancer Institute (NCI) protocols (Surgery Branch protocol 09-C-0082; IND 13871; Pediatric Branch (Protocol 12-C-0112G; IND: 14985). Refer to the current KTE-X19 IB for additional description of the T-cell product.

2.6. Clinical Experience with Anti-CD19 CAR T Cells in Studies Conducted at the National Cancer Institute (NCI)

The same CAR construct used in KTE-X19-103 was previously evaluated at the NCI in children and young adults with r/r ALL {Lee 2015}; (clinicaltrials.gov number NCT01593696), and in adults with r/r B-cell malignancies {Kochenderfer 2015}; (clinicaltrials.gov number NCT00924326).

Refer to the current KTE-X19 IB and publications cited for details on the study design and the safety and efficacy outcomes observed in these studies.

2.7. KTE-C19-101 ZUMA-1 Experience

ZUMA-1 is a Phase 1-2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in adult subjects with refractory DLBCL, PMBCL, and transformed follicular lymphoma (TFL). The primary analysis for the study, which has been completed, was based on analysis of the data from 92 subjects in the phase 2 portion of the study who had the opportunity to be followed for at least 6 months after infusion of KTE-C19. The study met its primary endpoint: the objective response rate per International Working Group 2007 criteria {Cheson 2007} in these 92 subjects was 82% (95% CI: 72%, 89%), which was significantly higher than the pre-specified control rate of 20% ($p < 0.0001$; {Locke 2017}).

Refer to the current KTE-C19 IB for a summary of the safety and efficacy findings from this study.

2.8. KTE-X19-103 ZUMA-3 Phase 1 Experience

ZUMA-3 is a study of KTE-X19 in adults with r/r ALL (see Section 3). The DLT evaluation period of the study was completed with no DLTs observed in the 2 x 10^6 anti-CD19 CAR T cells/kg dose cohort. Additional subjects have been enrolled and treated in the phase 1 portion of the study at 1 x 10^6 anti-CD19 CAR T cells/kg and 0.5 x 10^6 anti-CD19 CAR T cells/kg. Forty-five patients were dosed in the Phase 1 portion of study across the 3 dose levels. Based on the risk-benefit ratio observed, the dose of 1 x 10^6 anti-CD19 CAR T cells/kg was considered the recommended Phase 2 dose.

Refer to the current KTE-X19 IB for a summary of the safety.

3. KTE-X19-103 STUDY DESIGN

3.1. General Study Design

ZUMA-3 is a Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with relapsed or refractory B-precursor ALL. In this study, relapsed or refractory is defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogenic SCT (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment).

During Phase 1, approximately 3-12 subjects with high burden [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for DLT will be assessed to evaluate the safety of KTE-X19. A SRT that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and make recommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19. Additionally, approximately 40 subjects with high or low burden disease may be enrolled to further assess safety (see Figure 1 and Section 9.6).

During Phase 2, approximately 50 subjects in the mITT set will be assessed to evaluate the efficacy and safety of KTE-X19.

In total, up to approximately 100 subjects may be enrolled and treated with KTE-X19 in the study in Phase 1 and 2 combined (see Section 9.6 and Section 10.5).

During Phase 2, one interim and one primary analysis will be performed. The interim analysis is for safety only and will be performed by an independent DSMB after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion (see Section 10.7). Additional interim analyses for safety may be requested by the DSMB.

The primary analysis will occur when the overall study enrollment is complete and the last treated subject in the mITT set has had the opportunity to complete the month 6 disease assessment (see Section 10.8).

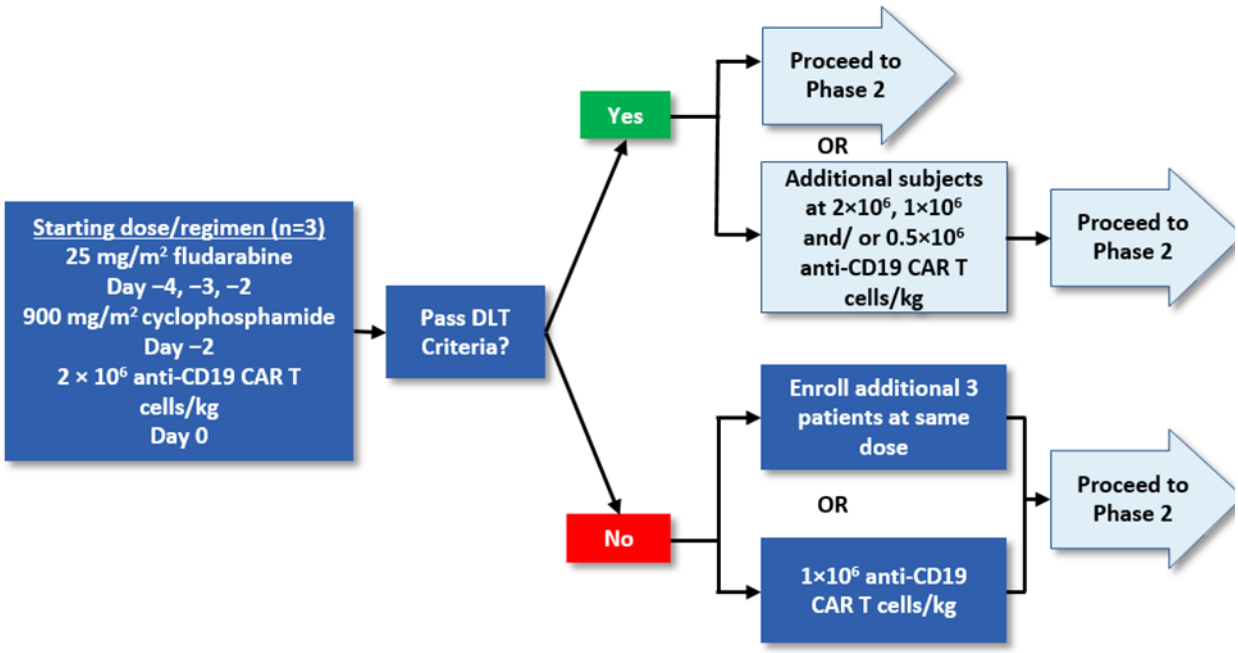
Each subject will provide consent and be evaluated for study participation. Once deemed eligible and enrolled into the study, each subject will follow the same study treatment schedule and procedural requirements, independent of the phase of the study, and proceed through the following study periods:

- Screening period
- Enrollment/Leukapheresis period
- Bridging chemotherapy and CSF prophylaxis period

- Conditioning chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long term follow-up period

For study requirements assigned to each study period, refer to the schedule of assessments (SOA) and Section 7 for details. A study schema is drawn out and described at the end of the protocol synopsis section.

Figure 1. Phase 1 Dosing



3.2. Participating Sites

Approximately **35** centers located in North America, Europe, and potentially other regions will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

Sites that do not enroll a subject within 4 months of site activation may be considered for closure.

3.3. Number of Subjects

Participants in this trial will be referred to as "subjects". Up to approximately 100 subjects may be enrolled into the entire study in order to obtain 3-12 subjects evaluable for DLT in the Phase 1 portion, up to approximately 40 additional Phase 1 subjects, and approximately 50 subjects in the mITT set in the Phase 2 portion of the study.

It should be noted that Kite Pharma may choose to close enrollment at any time. Refer to the statistical considerations section of the protocol for sample size estimations.

3.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified numbers of subjects are attained in the DLT evaluable (Phase 1) and mITT sets (Phase 2).

Subjects who have not received the required dose of KTE-X19 in order to be included in DLT evaluable set will be retained in the analyses of disposition and safety, where appropriate (see Section 10.5).

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and, if applicable, timing of transition to the separate Long-term Follow-up (LTFU) study, KT-US-982-5968 (refer to section 3.5.3).

The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects.

3.5.2. Completion of Study

Completion of the study is defined as the time at which every subject has completed at least 24 months of assessments, is considered lost to follow-up, withdraws consent, or dies. Upon activation of KT-US-982-5968 LTFU study at the subject's study site, subjects who received infusion of KTE-X19 will be offered the opportunity to complete LTFU assessments under the KT-US-982-5968 protocol.

3.5.3. Long-term Follow-up Period

All subjects who received an infusion of KTE-X19 will be provided the opportunity to transition to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to KTE-X19 as defined in KT-US-982-5968, presence of replication-competent retrovirus (RCR) and/or insertional mutagenesis for up to 15 years from the time of KTE-X19 infusion (also refer to section 7.11.9)

In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

4. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the IRB/IEC approved consent form before initiating any study specific procedures or activities that are not part of a subject's routine care. Refer to Section 7 for details.

Each subject who enters the screening period will receive a unique subject identification number at the time of consent [refer to the Investigational Product Manual (IPM)]. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject.

Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened.

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

101) Relapsed or refractory B-precursor ALL defined as one of the following:

- Primary refractory disease
- First relapse if first remission ≤ 12 months
- Relapsed or refractory disease after two or more lines of systemic therapy
- Relapsed or refractory disease after allogeneic transplant provided subject is at least 100 days from stem cell transplant at the time of enrollment and off of immunosuppressive medications for at least 4 weeks prior to enrollment

102) Morphological disease in the bone marrow (> 5% blasts)

103) Subjects with Ph^+ disease are eligible if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they have relapsed/refractory disease despite treatment with at least 2 different TKIs

104) Age 18 or older

105) Eastern cooperative oncology group (ECOG) performance status of 0 or 1

106) ANC ≥ 500/μL unless in the opinion of the PI cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy

107) Platelet count ≥ 50,000/μL unless in the opinion of the PI cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy

108) Absolute lymphocyte count ≥ 100/μL

109) Adequate renal, hepatic, pulmonary and cardiac function defined as:

- Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min
- Serum ALT/AST ≤ 2.5 x ULN (upper limit normal)
- Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome.
- Left ventricular ejection fraction (LVEF) ≥ 50%, no evidence of pericardial effusion as determined by an ECHO, no NYHA class III or class IV functional classification, and no clinically significant arrhythmias
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air

110) Females of childbearing potential must have a negative serum or urine pregnancy test

111) In subjects previously treated with blinatumomab, CD19 tumor expression on blasts obtained from bone marrow or peripheral blood must be documented after completion of the most recent prior line of therapy. If CD19 expression is quantified, then blasts must be ≥ 90% CD19 positive.

5.2. Exclusion Criteria

201) Diagnosis of Burkitt's leukemia/lymphoma according to WHO classification or chronic myelogenous leukemia lymphoid blast crisis

202) History of malignancy other than non-melanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease free for at least 3 years

203) History of severe hypersensitivity reaction to aminoglycosides or any of the agents used in this study

204) CNS abnormalities

- Presence of CNS-3 disease defined as detectable cerebrospinal blast cells in a sample of CSF with ≥ 5 WBCs per mm^3 with or without neurological changes, and
- Presence of CNS-2 disease defined as detectable cerebrospinal blast cells in a sample of CSF with <5 WBCs per mm^3 with neurological changes
  Note: Subjects with CNS-1 (no detectable leukemia in the CSF) and those with CNS-2 without clinically evident neurological changes are eligible to participate in the study.
- History or presence of any CNS disorder such as a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome (PRES), or cerebral edema

205) History of concomitant genetic syndrome associated with bone marrow failure such as Fanconi anemia, Kostmann syndrome, Shwachman-Diamond syndrome

206) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment

207) History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment.

208) Primary immunodeficiency

209) Known infection with HIV, hepatitis B or hepatitis C virus. A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.

210) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring antimicrobials for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite Medical Monitor

211) Prior medication:

- Salvage systemic therapy (including chemotherapy, TKIs for Ph^+ ALL, and blinatumomab) within 1 week or 5 half-lives (whichever is shorter) prior to enrollment
- Prior CD19 directed therapy other than blinatumomab
- History of CTCAE grade 4 neurologic event or grade 4 CRS {Lee 2014} with prior CD19-directed therapy
- Treatment with alemtuzumab within 6 months prior to enrollment, clofarabine or cladribine within 3 months prior to enrollment, or PEG-asparaginase within 3 weeks prior to enrollment
- Donor lymphocyte infusion (DLI) within 28 days prior to enrollment
- Any drug used for GVHD within 4 weeks prior to enrollment (eg, calcineurin inhibitors, methotrexate, mycophenolyate, rapamycin, thalidomide), or immunosuppressive antibody used within 4 weeks prior to enrollment (eg, anti-CD20, anti-tumor necrosis factor, anti-interleukin 6 or anti-interleukin 6 receptor)
- At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy prior to enrollment (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists etc)
- Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to enrollment

212) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Ommaya reservoirs and dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted

213) Acute GVHD grade II-IV by Glucksberg criteria or severity B-D by IBMTR index; acute or chronic GVHD requiring systemic treatment within 4 weeks prior to enrollment

214) Live vaccine ≤ 4 weeks prior to enrollment

215) Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

216) Subjects of both genders of child-bearing potential who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-X19

217) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

218) History of autoimmune disease (eg, Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

6. PROTOCOL TREATMENT

6.1. Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- Bridging chemotherapy refers to treatment used to control a subject's disease prior to conditioning chemotherapy.
- CSF prophylaxis will be administered prior to infusion of conditioning chemotherapy.
- The Conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The investigational product for this study is named KTE-X19.

6.2. Leukapheresis (within approximately 5 days of eligibility confirmation)

Before leukapheresis commences, the criteria outlined in Section 7.11.3 must be met.

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacture of KTE-X19. Leukapheresed cells obtained from subjects at participating centers will be shipped to the Cell Processing Facility (CPF) overnight as described in the IPM.

Mononuclear cells will be obtained by leukapheresis (approximately 12-15 liter apheresis with a goal to target approximately 5-10 x 10^9 mononuclear cells). The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the IPM.

Upon arrival at the CPF, each subject's leukapheresed product will be processed to positively select for T cells, which are then activated and transduced with a retroviral vector to introduce the CAR gene. The engineered T cells are then further expanded and cryopreserved to generate the investigational product per CPF standard operating procedures. After KTE-X19 has been manufactured and has passed release criteria, it will be shipped to the treating facility and must be stored per the IPM (see Section 6.6).

See Section 6.8 for excluded medications prior to leukapheresis.

6.3. Bridging Chemotherapy

Bridging therapy may be administered after leukapheresis and prior to conditioning chemotherapy at the investigators discretion. Bridging chemotherapy is recommended for all subjects particularly those subjects with high disease burden at baseline [M3 marrow (>25% leukemic blasts) or ≥ 1000 blasts/mm^3 in the peripheral circulation]. If prescribed, bridging chemotherapy must be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy.

Allowed bridging chemotherapy regimens are outlined in Table 2. Doses listed are recommended, and can be adjusted for age/comorbidities or per local or institutional guidelines.

Table 2. Bridging Chemotherapy Regimens

Bridging Chemotherapy Regimen [a]	
Attenuated VAD: Vincristine non-liposomal (1-2 mg IV weekly) or liposomal (2.25 mg/m^2 IV weekly), and dexamethasone 20-40 mg IV or PO daily x 3-4 days per week. Optional doxorubicin 50 mg/m^2 IV x 1 (first week only).	DOMP: Dexamethasone 6 mg/m2/day PO (or IV) divided BID days 1-5, vincristine 1.5 mg/m2 (maximum dose 2 mg) IV on day 1, methotrexate 20 mg/m2 PO weekly, 6-MP 50-75mg/m2/day PO daily
Mercaptopurine (6-MP): 50-75 mg/m^2/day by mouth (administer at bedtime on an empty stomach to improve absorption)	Attenuated FLAG/FLAG-IDA: fludarabine 30 mg/m^2 IV days 1-2, cytarabine 2 g/m^2 IV days 1-2, G-CSF 5 µg/kg SC or IV starts on day 3 and can continue until day before the start of conditioning chemotherapy. With or without idarubicin 6 mg/m^2 IV days 1-2.
Hydroxyurea: Doses titrated between 15-50 mg/kg/day (rounded to the nearest 500 mg capsule and given as a single daily oral dose on a continuous basis)	Mini-hyper CVAD (courses A and/or B): Course A: Cyclophosphamide 150 mg/m^2 q 12 hrs x 3 days, dexamethasone 20 mg/d IV or PO daily days 1-4 and 11-14, vincristine 2 mg IV x 1 Course B: methotrexate 250 mg/m^2 IV over 24h on day 1, cytarabine 0.5 g/m^2 IV q12h x 4 doses on days 2 and 3.

a Use of a TKI in combination with any of the above regimens is allowed for subjects with Ph$^+$ ALL and Ph-like ALL

Given subjects with r/r ALL can have rapidly progressive disease and clinical deterioration, bridging chemotherapy allows physicians to provide standard of care to subjects in the period between leukapheresis and manufacturing of KTE-X19. Based on the published data {Davila 2014, Lee 2014, Maude 2014}, decreased tumor burden is additionally associated with less cytokine release syndrome (CRS).

Bridging therapy should be administered per institutional guidelines.

Refer to the current product label for guidance on packaging, storage, preparation, administration, including necessary dose reductions for organ dysfunction, and toxicity management associated with the administration of chemotherapy agents.

6.4. CSF Prophylaxis

All subjects will receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose).

CSF prophylaxis will be administered any time during screening (eg, at time of screening lumbar puncture) through 7 days prior to KTE-X19 infusion.

Subjects who are enrolled with CNS-2 disease at baseline must receive CSF prophylaxis after leukapheresis and at least 7 days prior to KTE-X19 infusion, unless otherwise approved by the Kite Medical Monitor.

Multiple doses of CSF prophylaxis can be given per investigator discretion in accordance with institutional guidelines, but at least 7 days must pass between the last dose of CSF prophylaxis and KTE-X19 infusion.

Additional CSF prophylaxis may be given post-KTE-X19 infusion per investigator discretion in accordance with institutional guidelines, but should be avoided for at least 8 weeks after KTE-X19 infusion if possible.

Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, administration of CSF prophylaxis through the reservoir is acceptable.

6.5. Conditioning Chemotherapy

Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of KTE-X19. Subjects will receive conditioning chemotherapy from Day -4 through day -2.

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted.

Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of chemotherapy agents.

The investigational medicinal product (KTE-X19) must be available before initiation of conditioning chemotherapy.

See Section 7.11.6.1 for conditioning chemotherapy procedures.

6.5.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

6.5.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges from 3-12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

6.5.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient in mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$. Mesna will be administered around the cyclophosphamide dose according to institutional standards.

6.5.4. Rationale for Conditioning Chemotherapy Choice and Dose

The rationale for the conditioning chemotherapy regimen and dose selection is based on the Phase 1 study conducted at the Pediatric Oncology Branch at the NCI {Lee 2015}. In this study, 21 subjects (20 with ALL) were treated and all received the same fludarabine and cyclophosphamide schedule with a favorable benefit/risk profile.

Consistent with the NCI protocol {Lee 2015}, the KTE-X19-103 study will use the same Conditioning chemotherapy regimen consisting of fludarabine at a dose of 25 mg/m^2/day IV over 30 minutes on Day -4, Day -3, Day -2 prior to KTE-X19 and cyclophosphamide at a dose of 900 mg/m^2/day IV over 60 minutes on Day -2 prior to KTE-X19. Day -1 will be a rest day. The 3-day conditioning chemotherapy regimen may be administered in an outpatient setting in accordance with the daily dosing instructions outlined in Section 7.11.6.2.

Following completion of each subjects' conditioning chemotherapy regimen, subjects will receive their respective KTE-X19 infusion.

6.6. KTE-X19

The IP for this study is KTE-X19.

Refer to the most current Investigator's Brochure regarding KTE-X19 and clinical experience. This section contains general information and is not intended to provide specific instructions. Refer to the IPM for details and instruction on storage and administration of KTE-X19.

KTE-X19 is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing KTE-X19 arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

KTE-X19 is a subject-specific product and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of KTE-X19 infused, the thaw start/stop time, and KTE-X19 infusion start/stop time, will be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion.

To date, subjects have received doses of anti-CD19 CAR T cells ranging from 0.5 - 30 x 10^6 anti-CD19 CAR T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity (see Section 6.8 for more information related to corticosteroid use).

6.6.1. Rationale for KTE-X19 Dose

The rationale for the initial dose of KTE-X19 evaluated in ZUMA-3 (2 x 10^6 anti-CD19 CAR T cells/kg) was based on the DLT and MTD data generated from the 2 studies conducted at the Pediatric Oncology {Lee 2015} and Surgery Branch {Kochenderfer 2015} of the NCI. Additional doses evaluated in this study are further informed by emerging Phase 1 data (see Section 2.8).

In the Pediatric Oncology Branch study, 4 pediatric subjects were enrolled and received a starting dose of 1 x 10^6 anti-CD19 CAR T cells/kg with no DLT observed. The CAR T cell dose was then escalated to 3 x 10^6 anti-CD19 CAR T cells/kg. At this higher dose, 4 pediatric subjects were treated and 2 subjects experienced a CRS DLT (one Grade 3 and one Grade 4 event). Based on these observations, the study defined the MTD at 1 x 10^6 anti-CD19 CAR T cells/kg for the remainder of the study.

In the Surgery Branch adult study, as of November 30, 2014, Group 3 enrolled 11 adult subjects, where the first 7 and last 4 subjects received anti-CD19 CAR T cell infusion of 1 x 10^6 anti-CD19 CAR T cells/kg and 2 x 10^6 anti-CD19 CAR T cells/kg, respectively and the benefit/risk profile remained favorable.

In the ZUMA-3 study, the initial 6 subjects were treated at 2 x 10^6 anti-CD19 CAR T cell/kg, with a subsequent group of 14 subjects treated at 1 x 10^6 anti-CD19 CAR T cell/kg. No DLTs were observed in the DLT evaluable set, no drop off was seen in efficacy between the 2 x 10^6 anti-CD19 CAR T cell/kg and 1 x 10^6 anti-CD19 CAR T cell/kg KTE-X19 doses, and there was no clear difference in the safety profile (Section 2.8; {Shah 2016}). These data suggested it may be possible to lower the KTE-X19 dose further without diminishing and potentially enhancing the risk:benefit profile of KTE-X19 in r/r ALL. As a result, additional subjects were dosed at 0.5 x 10^6 anti-CD19 CAR T cells/kg. The safety profile observed at the lower dose was considered manageable, however the efficacy was diminished compared to higher dose levels. Based on the safety/efficacy observations, the SRT decision was to explore the safety profile at the 1 x 10^6 anti-CD19 CAR T cell/kg with implementation of new toxicity management recommendations by enrolling additional subjects at this dose level. The new safety profile observed at the dose of 1 x 10^6 anti-CD19 CAR T cell/kg was considered favorable without significant decrease in efficacy, therefore the dose of 1 x 10^6 anti-CD19 CAR T cell/kg was considered the recommended Phase 2 dose.

For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 or 1 x 10^8 or 0.5 x 10^8 anti-CD19 CART cells may be administered. See Sections 9.6 for details. If any problems related to the use of KTE-X19 or any products that support the successful delivery and infusion of KTE-X19 (eg, cryostorage bags, subject identification labels) required in this study are identified, refer to the instructions in the IPM for details).

6.7. Concomitant Therapy

Concomitant therapy refers to treatment that subjects receive during the conduct of the study.

Investigators may additionally prescribe any other concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF) and routine anti-emetic prophylaxis and treatment except those medications listed in the excluded medication Section 6.8.

In subjects with Ph^+ disease and who achieve **CR**, a TKI may be resumed 2 months after KTE-X19 infusion at the investigator discretion and in accordance with institutional guidelines. See Section 3, Table 2 for use of TKI's during bridging chemotherapy.

The investigator is responsible for reporting all concomitant medications as follows in Table 3:

Table 3. Reporting Requirements for Concomitant Medications

Subjects who are pre-screen or screen-fails	Subjects who are enrolled, but do not receive KTE-X19 infusion	Subjects who are enrolled and receive KTE-X19 infusion
• Concomitant therapies related to serious adverse event(s) will be recorded from the date of the pre-screening informed consent or screening informed consent through 30 days after the last study-specific pre-screening or screening procedure, respectively.	• Concomitant therapies will be recorded from the date of the informed consent until 30 days after the last study-specific procedure has occurred (eg, leukapheresis, conditioning chemotherapy) or until the initiation of new anti-cancer therapy, whichever occurs first.	• Concomitant therapies including medications, intubation, dialysis, oxygen, and blood products will be recorded from the date of the informed consent until 3 months after completing treatment with KTE-X19. (excluding allogeneic SCT) • After this 3-month follow-up period, targeted concomitant therapies will be recorded for either 24 months after KTE-X19 infusion or until disease progression, whichever occurs first. o Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations. o In subjects who received allogeneic SCT, only concomitant medications related to a KTE-X19-related serious adverse event (SAE) will be recorded. Reporting of these concomitant medications will commence at the time the SCT preparative regimen commences.

See Section 6.9 regarding documentation of subsequent anticancer therapy.

6.8. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 infusion.

Systemic corticosteroids should be avoided as premedication in subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). If possible, such subjects should undergo non-contrast CT scans or alternative imagine modality (such as MRI) instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after KTE-X19 infusion, unless used to manage KTE-X19 related toxicities (Refer to the most current version of the IB; see Section 6.4). Other medications which may interfere with evaluation of KTE-X19, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

Therapeutic doses of systemic anticoagulants, such as unfractionated heparin and low-molecular weight heparin, should be avoided anytime subjects are at risk of bleeding due to thrombocytopenia when possible. If a subject requires the initiation of therapeutic anticoagulant doses prior to initiation of conditioning chemotherapy or prior to KTE-X19 infusion, then conditioning chemotherapy/KTE-X19 infusion must be held and the case discussed with the Kite Medical Monitor.

For subjects with Ph^+ ALL, all TKIs must be stopped at least 1 week prior to KTE-X19 infusion, including but not limited to imatinib, dasatinib, and ponatinib. In subjects who achieve CR, a TKI may be resumed 2 months after KTE-X19 infusion. See Section 6.3, Table 2 for use of TKIs during bridging chemotherapy.

CSF prophylaxis may be given post-KTE-X19 infusion per investigator discretion in accordance with institutional guidelines, but should be avoided for at least 8 weeks after KTE-X19 infusion if possible.

Treatment for the subject's leukemia such as chemotherapy, immunotherapy, targeted agents, radiation, high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited except as needed for treatment of disease progression after KTE-X19 infusion. If permissibility of a specific medication/treatment is in question, contact the Kite Pharma medical monitor.

Medications with sedative properties should be avoided if possible in the setting of neurologic events (refer to the KTE-X19 IB).

6.9. Subsequent Therapy

Subsequent therapy administered after KTE-X19 infusion for a subject's disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy will be recorded for all enrolled subjects until one of the following occurs: subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, dies, or transitions to the KT-US-982-5968 LTFU study where subsequent therapy will continue to be recorded.

For subjects who are enrolled, but do not receive KTE-X19 infusion, any additional anti-cancer therapy will also be collected until the subject completes their participation in the current study, is considered lost to follow up, withdraws consent, or dies, whichever occurs first.

6.10. Toxicity Management

To date, the following important risks have been identified with KTE-X19: CRS, neurological events, infections, and cytopenias. Refer to the current KTE-X19 IB for details regarding these events and management guidance.

As the safety experience with KTE-X19 increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the KTE-X19 IB for guidance regarding managing KTE-X19 related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with KTE-X19 as well as possible complications associated with malignancy and cancer treatment.

7. STUDY PROCEDURES

Research staff should refer to the SOA for an outline of the procedures required. The visit schedule is calculated from KTE-X19 infusion on Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7.11. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved Informed Consent form (ICF) prior to any study specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

7.2. Demographic Data

Demographic data will be collected per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity and country of enrollment to study their possible association with subject safety and treatment effectiveness.

7.3. Medical and Treatment History

Relevant medical history prior to the start of adverse event reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the subject's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subject's chart should be obtained.

7.4. Physical Exam, Vital Signs, Performance Status, and European Quality of Life-5 Dimensions (EQ-5D)

Physical exams will be performed during screening and at times noted in the SOA. Changes noted in subsequent exams when compared to the baseline exam will be reported as an adverse event.

During KTE-X19 infusion/hospitalization, vital signs including blood pressure, heart rate, oxygen saturation, and temperature will be monitored before and after the KTE-X19 infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3^{o}C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

Performance status as measured by the ECOG scale will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

The EQ-5D will be completed only for subjects participating in phase 2. The EQ-5D will be completed at the timepoints outlined in the SOA prior to other study related procedures or assessments. Subjects who are blind or illiterate may have the EQ-5D questions read to them by the study staff. The study staff, however, cannot interpret any of the questions for the subject. A subject may be exempt from completing the questionnaire if he or she is unable to read the questionnaire in one of the country languages available.

The EQ-5D is a 2 page generic patient questionnaire for assessing the overall health status of a subject. The EQ-5D consists of a 5 dimension descriptive system including questions on mobility, self-care, usual activities, pain/comfort, and anxiety/depression and a visual analogue scale (EQ VAS) which allows the respondent to record health on a vertical scale (eg, best health to worst health) thus allowing a quantitative measure of health outcome.

7.5. Neurological Assessment

Subject's neurological status should be evaluated at screening to establish a baseline. After enrollment, subjects should be evaluated for any neurological symptoms at each of the timepoints specified in the SOA. During the hospitalization period, evaluations of neurological status may need to be increased. Changes in neurological status should be reported as an adverse event per Section 9.

7.6. Cardiac Function

Each subject's cardiac function as measured by ECHO will be assessed during the screening period to confirm study eligibility. No evidence of pericardial effusion, as required by eligibility, will also be confirmed by ECHO.

If the last chemotherapy regimen the subject received is not considered cardiotoxic, then an ECHO performed within 28 days prior to signing the consent may be used for eligibility.

If the last chemotherapy regimen the subject received is considered cardiotoxic, then an ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

A baseline chest x-ray will be completed within 14 days before enrollment to confirm eligibility.

To establish a baseline, an ECG will be performed within 30 days before enrollment.

7.7. Lumbar Puncture

CSF samples (ie, collected on or after informed consent) will be analyzed locally for disease assessment (see Section 7.8 for details regarding analytes). A portion will be submitted to the central laboratory for disease assessment and toxicity evaluation. Refer to refer to the KTE-X19 IB regarding platelet support.

Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, withdrawal of the CSF sample through the reservoir is acceptable.

CSF samples will be collected at the following time points:

- Baseline – a CSF result obtained within 30 days before enrollment will be acceptable for eligibility determination
- At the time of CSF prophylaxis (this sample may be the same as the baseline sample)
- For subjects with CNS-2 at baseline, a CSF sample is required at the time of first presumed response (ie, bone marrow blasts < 5%)
- First onset of ≥ grade 2 neurological symptoms or as medically indicated
- Additional evaluations of the CSF should be performed per institutional standard of care

CSF blast counts can be falsely increased in cases of traumatic lumbar puncture. In this instance, the blast count should be adjusted using the following formula, and the corrected value entered into the CRF:

$$blast(CSF, true) = blast\ (CSF, observed) - blast\ (blood)\ \times \frac{RBC(CSF)}{RBC(blood)}$$

Subjects with CNS-2 will have a lumbar puncture performed at the screening visit for examination of CSF. In addition, a lumbar puncture may be performed as applicable for subjects with new onset of a Grade 2 or higher neurologic event after KTE-X19 infusion

7.8. Laboratory

The below samples will be collected at the time points indicated in the SOA. Additional samples (eg, blood, urine, other bodily fluids, tissue) may be collected as needed for further safety testing.

Local Laboratory Analysis:

- Bone marrow evaluation for % blasts
- Cerebral spinal fluid (total protein, WBC, RBC, %blast by morphological assessment, and gram stain and culture if clinically indicated or for neurological event)
- Sodium (Na), Potassium (K), Chloride (Cl), Total CO_2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN) or Urea (if BUN not available), Albumin, Calcium (Ca) total, Magnesium total (Mg), Inorganic Phosphorus (P), Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LDH, Uric Acid (Note: Direct Bilirubin, LDH, and Uric Acid are recommended, not mandatory)
- C-reactive protein
- Complete Blood Count with differential (5-part preferred, but 3-part will be acceptable)
- Peripheral blast count recommended (see Section 7.11.6.3 regarding Day -4)
- Absolute lymphocyte count (ALC)
- CD3 count based on peripheral blood
- CD19 immunophenotyping by flow cytometry or IHC using peripheral blood or bone marrow
  - Note: Surface CD19 expression should be measured by flow cytometry; IHC analysis is allowed if the bone marrow aspirate is a dry tap, inadequate or there were insufficient circulating blasts for flow cytometry.
- A urine or serum sample will be collected for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma medical monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma Medical Monitor for instructions.
- For European Union (EU) sites, viral serologic tests (eg, HIV, hepatitis B, hepatitis C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis (see Section 7.11.1).

Central Laboratory Analysis:

- Bone marrow biopsy and aspirate samples collected for confirmation of diagnosis as well as disease assessment
- Cerebral spinal fluid

- Blood draws for cytokine levels and PBMCs (for the analysis of lymphocyte subsets, anti-CD19 CART cells, and replication-competent retrovirus [RCR] analysis)
- Serum samples will also be drawn for anti-KTE-X19 antibodies
- Peripheral blood
- See central laboratory manual for details.

7.9. Disease Assessments

7.9.1. Bone Marrow Evaluation

Bone marrow aspirates and biopsies will be collected throughout the study per the protocol SOA and/or standard of care.

- Screening bone marrow evaluation:
  - If available, archival formalin-fixed paraffin embedded (FFPE) bone marrow block and/or slides used for the original diagnosis of ALL will be submitted to the central laboratory along with the pathology report.
  - A bone marrow aspirate and biopsy is required at screening and will be performed after the last dose of systemic chemotherapy and within approximately 14 days before enrollment to establish baseline disease.
    - If there is a delay between when the screening bone marrow is performed and the apheresis, contact the Kite Medical Monitor for guidance on whether or not bone marrow evaluation needs to be repeated. If a fresh bone marrow aspirate and biopsy was recently collected and properly stored prior to consent, then contact the Kite Medical Monitor to confirm if this sample is adequate for screening.
  - In subjects who receive bridging chemotherapy, an additional bone marrow sample is required between the end of bridging chemotherapy and Day -4. If bridging chemotherapy is not administered, then the additional bone marrow sample is not required, however, an assessment of peripheral circulating blasts is required (see Section 7.11.6.3 regarding requirement for peripheral blast count).
- On study bone marrow evaluations:
  - A bone marrow aspirate will be required at all time points per the SOA to assess treatment response.
    - For subjects who undergo a SCT, bone marrow evaluations are not required during the first 100 days post-SCT. After 100 days, bone marrow evaluations should be performed at the next per protocol time point per the SOA. If a subject has a bone marrow evaluation earlier than the next per protocol time point, then the bone marrow samples should be processed and submitted to the central laboratory per the central laboratory manual.

- In addition to the bone marrow aspirate, a bone marrow biopsy is required at Day -4 and Day 28. A bone marrow biopsy at all other time points is recommended and should be performed if standard of care. Note: Anytime the bone marrow aspirate is a dry tap, then a bone marrow biopsy is required. In the case of a dry tap, the bone marrow biopsy will be used to determine disease burden by immunohistochemical (IHC) analyses. The following markers will be analyzed by IHC: CD10, CD19, CD20, CD34, Pax5 and TdT.
- CCI [redacted]
- Reminders:
  - For subjects with a CR, collection and analysis of CSF is required to confirm CR (see Section 7.7)
  - For subjects with PD, a PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy

Locally evaluated % blasts from the bone marrow evaluation and if available local MRD will be entered to the CRF.

Overall response will be assessed by the investigator per Appendix 1. If bone marrow blasts are $\leq$ 5% and circulating blasts are $\geq$ 1%, then additional studies (eg, flow cytometry) should be performed to quantify the blasts.

Bone marrow aspirate and biopsy samples will be processed and submitted to the central laboratory as outlined in the central laboratory manual. Refer to the laboratory manual for collection, processing and shipment requirements; note some samples, eg, MRD, must be shipped on the same day of collection. Below is an overview of the sample types that will be required.

Samples from bone marrow aspirate may include:

- MRD assessment
- Stained slide smears
  - The same slides used to evaluate ALL disease status (eg, % blasts) locally will be submitted to the central laboratory and will then be returned back to the investigative site after the review is completed. If the same slides used to diagnose ALL cannot be submitted to the central laboratory per institutional policy, then slides from the same procedure should be submitted. See central laboratory manual for details.
- Bone marrow mononuclear cells

Samples from bone marrow biopsy may include:

- Touch prep slide
- Core biopsy in formalin, formalin-fixed paraffin embedded block, or unstained slides

The corresponding pathology report should be submitted to the central laboratory along with the archival and on-study bone marrow samples.

7.9.2. Imaging Requirements (Only Applies to Subjects with Known Non-CNS Extramedullary Disease at Baseline)

- Extramedullary disease will be assessed prior to baseline with an imaging modality appropriate for the anatomical site and clinical scenario (eg, MRI for CNS lesion, ultrasound for testicular lesion, CT for intra-abdominal or thoracic lesion).
  - For all subjects with known non-CNS extramedullary disease, images must be taken within 28 days before conditioning chemotherapy. In addition, for subjects receiving bridging chemotherapy, images must be taken after bridging chemotherapy has completed.
- Following KTE-X19 infusion, the first on study images will occur at the time of first presumed response (ie, bone marrow blasts ≤ 5%)
- Subsequent images will continue as per the SOA through Month 24 or disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then images will be performed per standard of care until disease progression.
- All on-study assessments of extramedullary disease detected through imaging should be made with the same imaging modality and of the same anatomical locations as imaged at baseline.
- Response is evaluated by the investigator (Appendix 1).
- For all subjects, images should be performed per standard of care anytime the subject presents with symptoms suggestive of disease progression even if it is off schedule as per the SOA.
- Images will be submitted to a central imaging vendor; central imaging vendor manual to be provided separately.

7.10. Biomarkers

Biomarker analysis will be performed on blood and bone marrow derived tumor samples to evaluate predictive and pharmacodynamic markers for KTE-X19. Prognostic markers specific for B-ALL and related to the tumor immune environment may also be evaluated.

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR T cells will be monitored in the blood and bone marrow by flow cytometry. Expansion and persistence in peripheral blood will also be monitored by a CD19 CAR specific droplet digital chain reaction assay (ddPCR).

Levels of serum cytokines and chemokines will be evaluated in the blood and CSF. The analysis of cytokines and chemokines in the CSF will be performed at baseline and post-anti-CD19 CAR T cell infusion in subjects who present with first onset of ≥ grade 2 neurologic events. An additional sample for serum cytokine and chemokine analysis should be drawn at first onset and first reoccurrence of any > grade 2 CRS (per Lee 2014 criteria; Table 15) if not already collected on that day. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines IL-6, TNFα, IL-8, IL-1, IL-2, GM-CSF, IL-15, IL-17a, IFNγ, IL-12p40/p70; immune effector molecules Granzyme A, B, Perforin, sFasL; correlates of acute phase response C-reactive protein (CRP), SAA and Chemokines MIP-1α, MIP-3α, IP-10, Eotaxin, MCP-4.

Cerebrospinal fluid (CSF) as well as any additional subject samples (eg, pleural fluid) may be collected from subjects who develop neurologic events or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable lymphocyte populations residing in the CSF or other additional subject samples may also be analyzed for the purpose of understanding the safety profile of KTE-X19.

As KTE-X19 comprises retroviral vector transduced T cells, the presence of RCR in the blood of treated subjects will be monitored. Replication-competent retrovirus testing will occur at baseline, Month 3, Month 6, and Month 12. Thereafter, samples will be collected yearly and held for up to 15 years. If a subject tests positive for RCR at any time point within the first year, samples will continue to be collected and tested yearly for up 15 years or as clinically indicated. Baseline leukapheresis and final KTE-X19 samples will be banked and may be analyzed by immunophenotyping, quantitative polymerase chain reaction (qPCR) and/or gene expression profiling. CCI [redacted]

A pre-treatment bone marrow aspirate and biopsy will be collected for central pathology review, establishment of baseline protein and molecular markers for subsequent MRD assessment and evaluation of prognostic markers specific for B-ALL and also the tumor immune environment. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. CCI [redacted]

Monitoring of MRD to determine presence of residual leukemic blasts will be performed on bone marrow aspirates. Standard assessment of MRD utilizing multicolor flow cytometry or qPCR to detect residual cancerous cells with a sensitivity of 10^{-4}, will be accompanied by a more sensitive analysis utilizing next generation sequencing with a sensitivity of 10^{-6}. The latter detects clonal B-cell specific sequences that are shared across the malignant cell population. Given that clinical correlates of MRD status in B-ALL are based on a threshold of 10^{-4}, and clinical significance of identifying blasts at the 10^{-6} level is uncertain, the higher sensitivity analysis is for CCI [redacted] only and will not be used to derive the endpoint of MRD rate.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

7.11. Procedures by Study Period

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled or the reason for why the subject failed screening.

7.11.1. Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through enrollment. Informed consent must be obtained before completion of any study specific procedures. Procedures that are part of SOC are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA.

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled into the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA:

- Medical history (see Section 7.3)
- Physical examination including height and weight (see Section 7.4)
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- EQ-5D (Phase 2 subjects only; see Section 7.4)
- Neurological assessment (see Section 7.5)
- ECG (see Section 7.6)
- Left ventricular ejection fraction (LVEF) and pericardial effusion assessment (ECHO) (see Section 7.6)
- Labs (see Section 7.8)
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Chemistry panel
  - CBC with differential
  - Peripheral blood
  - CD19 immunophenotyping on peripheral blood or bone marrow aspirate
  - Lumbar puncture for collection of CSF (see Section 7.7)
  - For EU sites, viral serologic tests (eg, HIV, hepatitis B, hepatitis C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.
- CSF prophylaxis if indicated (see Section 6.4)
- Chest x-ray (not required if other imaging modalities are used for baseline assessment of chest)
- Disease assessment (see Section 7.7 and Section 7.9)

- Screening bone marrow evaluation:

  — If available, archival formalin-fixed paraffin embedded (FFPE) bone marrow block and/or slides used for the original diagnosis of ALL will be submitted to the central laboratory

  — A bone marrow aspirate and biopsy is required at screening and will be performed after the last dose of systemic chemotherapy and within approximately 14 days before enrollment to establish baseline disease.

    ■ If there is a delay between when the screening bone marrow is performed and the apheresis, contact the Kite Medical Monitor for guidance on whether or not bone marrow evaluation needs to be repeated. If a fresh bone marrow aspirate and biopsy was recently collected and properly stored prior to consent, then contact the Kite Medical Monitor to confirm if this sample is adequate for screening.

- Serious Adverse Event reporting (refer to Section 9)

- Concomitant medications documentation and previous cancer treatment history (see Section 6.7)

7.11.2. Rescreening

Subjects who are unable to complete or fail to meet the eligibility criteria during the 28-day screening period will be allowed to rescreen. Subjects will retain the same subject indentifcation number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, the assessment or procedure that initially resulted in the subject failing screening will be performed, including any other procedures that fell outside of the designated screening window (ie, lab assessments); all other initial screening procedures/assessments do not need to be repeated.

7.11.3. Enrollment/Leukapheresis

Before leukapheresis commences, the following criteria must be met:

- In general, all eligibility criteria confirmed during screening must not be known to be violated prior to leukapheresis. Additionally, the investigator must review and confirm that the last CBC with differential and chemistry panel drawn prior to the start of leukapheresis must meet the eligibility criteria detailed in Inclusion criterion 105. If any screening assessments or procedures are repeated between screening and the start of leukapheresis and results are outside the eligibility criteria (Section 5), contact the Kite medical monitor before proceeding with leukapheresis.

- Subjects must have no evidence of clinically significant infection prior to leukapheresis. Should a subject have clinically significant infection immediately prior to leukapheresis, cell collection must be delayed until the event resolves.

- If leukapheresis is delayed beyond 5 days, a CBC with differential and chemistry panel must be repeated.

- If WBC collected at time of leukapheresis is ≥ 50,000 cells/μL a contact must be made to the Kite Medical Monitor before proceeding with leukapheresis.

- Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis (see Section 6.8).

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

The following procedures/requirements will occur on the leukapheresis collection day (enrollment) and as outlined in the SOA:

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature

- Weight (weight must be collected on the day of leukapheresis)

- Labs (to be drawn prior to leukapheresis either on the day of or the day before leukapheresis) (see Section 7.8)

  — Chemistry Panel

  — C-reactive protein; if CRP is ≥ 100 mg/L, contact the Kite Medical Monitor before proceeding with Conditioning chemotherapy

  — CD3 count

  — CBC with differential

  — Anti-KTE-X19 antibody

  — Blood draw for PBMCs and cytokine levels

- Leukapheresis (see Section 6.2)

- Adverse/Serious Adverse Event reporting (refer to Section 9)

- Concomitant medications documentation (see Section 6.7)

Vitals, lab draws, adverse/serious adverse event reporting and concomitant medications documentation may be performed the day before leukapheresis, unless otherwise specified.

7.11.4. Bridging Chemotherapy Period

If prescribed, bridging chemotherapy will be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy (see Section 6.3).

The following procedures will be performed:

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy) (see Section 7.8)
  - Chemistry Panel
  - CBC with differential
- Bridging chemotherapy (see Section 6.3)
- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concomitant medications documentation (see Section 6.7)

Note: As appropriate, vitals and labs should be repeated each day bridging chemotherapy is administered.

7.11.5. CSF Prophylaxis Period

Intrathecal chemotherapy for CSF Prophylaxis will be administered any time during screening through 7 days prior to KTE-X19 infusion (see Section 6.4).

The following procedures will be performed:

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy) (see Section 7.8)
  - Chemistry Panel
  - CBC with differential
  - Lumbar puncture for collection of CSF (see Section 7.7)
- Intrathecal chemotherapy (see Section 6.4)
- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concomitant medications documentation (see Section 6.7)

Note: As appropriate, vitals and labs should be repeated each day CSF prophylaxis is administered.

7.11.6. Conditioning Chemotherapy and KTE-X19 Infusion

Administration of KTE-X19 cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion.

Signs, symptoms or abnormal laboratory results attributed to the malignancy (elevated C-reactive protein [CRP]) are diagnoses of exclusion that require a documented workup to establish. Conditioning chemotherapy and KTE-X19 infusion should only be initiated after it is reasonably assured that cell infusion can safely proceed.

The investigational medicinal product (KTE-X19) must be available before initiation of conditioning chemotherapy.

Refer to Section 7.11.7.5 for Requirements to Work-up Potential Infectious and/or Inflammatory States.

7.11.6.1. Conditioning Chemotherapy Period

7.11.6.1.1. Requirements for Initiating Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the work-up listed in Section 7.11.7.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38ºC within 72 hours before conditioning chemotherapy
- CRP > 100 mg/L any time between enrolment to start of conditioning chemotherapy
- WBC count or WBC differential concerning for infectious process between enrollment to start of conditioning chemotherapy (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally,

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy.
- Complete history and physical exam including HEENT, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of anti-microbials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable)

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with conditioning chemotherapy.

7.11.6.2. Conditioning Chemotherapy Administration (Day -4 Through Day -2 Prior to KTE-X19 Infusion)

Subjects will receive a conditioning chemotherapy regimen consisting of cyclophosphamide and fludarabine. The first dose of conditioning chemotherapy will be designated as Day –4. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day –4 and through Day –2, with 1 rest day (Day -1) before receiving KTE-X19. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

Conditioning chemotherapy (fludarabine and cyclophosphamide) will be supplied by the investigative site unless otherwise noted and should be administered per institutional guidelines. Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of chemotherapy agents.

Before conditioning chemotherapy commences, the criteria outlined in Section 7.11.6.1 must be met.

Provided the criteria for conditioning chemotherapy are met, the 3-day conditioning regimen of fludarabine and cyclophosphamide will be administered in accordance with the following daily dosing instructions:

- Subjects should receive IV hydration with conditioning chemotherapy per institutional guidelines or investigator discretion; recommendations for IV hydration are listed below:

- IV pre-hydration starting 90 minutes prior to fludarabine and continuing for at least 8 hours after with 0.45% sodium chloride and 5% dextrose (or other composition appropriate for the clinical situation) at a rate of at least 90 mL/m^2/hour. Hydration may be temporarily interrupted to give fludarabine or cyclophosphamide but should continue until at least 8 hours after the cyclophosphamide dose has been completed.

- Fludarabine 25 mg/m^2/day IV in 50 mL of 0.9% sodium chloride over 30 minutes on Day -4, Day -3, Day -2 followed by:

- Cyclophosphamide at a dose of 900 mg/m^2/day IV over 60 minutes on Day -2 only
- Add mesna per institutional guidelines
- Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (total fluids approximately 1.5 L/m^2/24 hours IV + PO). In general, subjects should be kept well hydrated but closely monitored to prevent fluid overload.
- Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours) if no contraindications. In general subjects should be kept well hydrated but closely monitored to prevent fluid overload.

7.11.6.3. Conditioning Chemotherapy Procedures

The following procedures will be completed during Day -4 to Day -2. Day -1 is a rest day.

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Labs (to be drawn prior to chemotherapy) (see Section 7.8)
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Chemistry Panel
  - CBC with differential
    - Note: If subject did not have bridging therapy and hence bone marrow is not collected between the end of bridging chemotherapy and start of Conditioning chemotherapy, then sites must assess peripheral blasts counts during this time period (eg, at Day -4).
  - Blood draw for PBMCs and cytokine levels
- Bone marrow evaluation (see Section 7.9.1)
  - In subjects who receive bridging chemotherapy, an additional bone marrow sample is required between the end of bridging chemotherapy and Day -4. If bridging chemotherapy is not administered, then the additional bone marrow sample is not required.
- Conditioning chemotherapy (Fludarabine and cyclophosphamide) administration (see Section 6.5)
- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concomitant medications documentation (see Section 6.7)

7.11.7. Investigational Product Treatment Period

7.11.7.1. Pre-KTE-X19 Infusion Criteria

If any of the following criteria are met prior to the initiation of KTE-X19, then the work-up listed in Section 7.11.7.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of KTE-X19 infusion
- CRP > 100 mg/L any time between enrollment to start of KTE-X19 infusion
- WBC count or WBC differential concerning for infectious process between enrollment to start of KTE-X19infusion (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally:

- All eligibility criteria of the protocol must be met. If any screening assessments or procedures are repeated between confirmation of eligibility and the start of KTE-X19 infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with KTE-X19 infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam including HEENT, and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before KTE-X19 (prophylactic use of anti-microbials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable).
- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with administration of KTE-X19.

If the KTE-X19 infusion is delayed > 2 weeks, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

7.11.7.2. Hospitalization for KTE-X19 Infusion

Subjects will be hospitalized to receive infusion of KTE-X19 followed by a minimum 7 day observation period unless otherwise required by country regulatory agencies (refer to Appendix 3 for details).

Subjects will remain in the hospital through day 7 post infusion of KTE-X19. Subjects should not be discharged from the hospital until all KTE-X19-related non-hematological toxicities return to grade ≤ 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg, renal insufficiency) even if > grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing KTE-X19-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > grade 1, or if deemed necessary by the treating investigator.

Given the possibility that a subject could develop CRS or neurologic events in the outpatient setting after discharge, subjects and their family members/caregivers should be educated on potential symptoms of these syndromes such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the principal investigator or seek immediate medical attention.

See Section 6.8 for excluded medications prior to and after KTE-X19.

7.11.7.3. KTE-X19 Premedication Dosing

The following pre-KTE-X19 infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the Kite medical monitor

- Acetaminophen 650 mg PO or equivalent
- Diphenhydramine 12.5 mg administered either orally or via IV or equivalent

7.11.7.4. KTE-X19 Infusion (Day 0)

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of KTE-X19. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of KTE-X19 are outlined in the IPM. It is recommended that vital signs are recorded before KTE-X19 infusion and then routinely as clinically indicated (eg, fever ≥ 38.3°C).

The IPM must be reviewed prior to administration of KTE-X19.

Research sites should follow institutional guidelines for the infusion of cell products.

During this period, the following procedures will be completed at the time points outlined in the SOA:

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature every Q4-6 hours during hospitalization (see Section 7.4 for vital sign requirements during the initial hospitalization)
- ECOG performance status
- EQ-5D (Phase 2 subjects only; see Section 7.4)
- Neurological assessment (see Section 7.5)
- Labs (before KTE-X19 infusion) (see Section 7.8)
  - Chemistry Panel
  - CBC with differential
  - Blood draw for PBMCs and cytokine levels (See SOA for frequency)
  - Recommended: Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regards to CRS/neurologic events. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continuing through hospitalization. In addition, lactate should be monitored as clinically indicated.
- Lumbar puncture for subjects with first onset grade ≥ 2 neurologic symptoms should be completed for examination of CSF (see Section 7.7)
- As applicable, an additional cytokine sample should be drawn at the first onset and first reoccurrence of any ≥ grade 2 CRS (per Lee 2014 criteria; Table 15) if not already collected on that day
- Bone marrow evaluation (see Section 7.9)
  - CCI [redacted]
- KTE-X19 pre-medications (see Section 7.11.7.3)
- Infusion of KTE-X19
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation (see Section 6.7)

7.11.7.5. Requirements to Work-Up Potential Infectious and/or Inflammatory States Prior to KTE-X19 Infusion

In the absence of an identified source of infection (eg, line infection, pneumonia on chest x-ray), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or KTE-X19 consists of:

- Call Kite medical monitor
- Infectious disease service consult (if applicable)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of anti-microbials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x2 bottles each) and UA and urine culture. Deep/induced sputum culture if clinically indicated.
  - All indwelling lines, such as central venous catheters, should be examined for any signs of infection, and additional cultures should be drawn from the line.
  - Nasopharyngeal-throat (NPT) swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus [CMV])
- If a central nervous system process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed.
- Any additional sign or symptom-directed investigation should be performed as clinically indicated.

Prior to proceeding with conditioning chemotherapy and/or KTE-X19 infusion, the above workup must not suggest the presence of an active infection, and all requirements for conditioning chemotherapy and/or KTE-X19 infusion must be satisfied. If the KTE-X19 infusion is delayed > 2 weeks following conditioning chemotherapy, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

- If the above workup was triggered due to CRP > 100 mg/L, CRP should be repeated, and if CRP continues to increase significantly, evaluation should be performed for any other potential infectious or inflammatory condition not previously evaluated.

7.11.8. Post-treatment Assessment Period

After completing KTE-X19 infusion and discharged from the hospital, all subjects will be followed in the post treatment assessment period. Counting from day 0 (KTE-X19 infusion), subjects will return to the clinic at the following intervals.

- Day 14 (± 2 days)
- Day 28 (+ 3 days)
- Week 8 (± 1 week)
- Month 3 (± 2 weeks)

Subject will allow key sponsor contacts to continue to access medical records so that information related to subjects health condition and initial treatment response may be obtained.

The following procedures will be completed for subjects as outlined in the SOA:

- Physical exam
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature
- EQ-5D (Phase 2 subjects only; see Section 7.4)
- Neurological assessment (see Section 7.5)
- Labs (see Section 7.8)
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Chemistry Panel
  - CBC with differential
  - Anti-KTE-X19 antibodies
  - Blood draw for PBMCs and cytokine levels
- Lumbar puncture for subjects with first onset grade ≥ 2 neurologic symptoms should be completed for examination of CSF (see Section 7.7)
- As applicable, an additional cytokine sample should be drawn at the first onset and first reoccurrence of any ≥ grade 2 CRS (per Lee 2014 criteria; Table 15) if not already collected on that day
- Disease Assessment (see Section 7.7 and Section 7.9)

- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concomitant medications documentation (see Section 6.7)

Following the initial hospitalization for the KTE-X19 infusion, if the subject is hospitalized with any KTE-X19 related adverse event, the following labs will be collected:

- PBMCs on day of admission, then weekly, and on day of discharge
- Cytokine levels on day of admission, then weekly, and on day of discharge

If a subject progresses before completion of the Month 3 visit, then the following procedures will be completed:

- Labs (if not already collected at visit in which progressive disease/relapse was confirmed):
  - Blood draw for PBMC
    - A PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy
  - Anti-KTE-X19 antibodies
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Proceed to the long term follow-up period (see Section 7.11.9 for details).

7.11.9. Long-term Follow-up Period

All enrolled subjects will be followed in the long term follow-up period for safety, survival and disease status, if applicable. Subjects will begin the long term follow-up period after they have completed the Month 3 visit of the post-treatment assessment period (whether they responded to treatment or went straight to the month 3 visit due to disease progression). After completion of the Month 24 visit, subjects who received an infusion of KTE-X19 will be provided the opportunity to transition to a separate LTFU study, KT-US-982-5968 (refer to section 3.5.3).

- Every 3 months (± 2 weeks) through Month 18
- Every 6 months (± 1 month) between Month 24 - Month 60
- Beginning with year 6, Month 72 (± 3 months), subjects will return to the clinic 1 time annually up to 15 years after the last subject receives their KTE-X19 infusion.

The following procedures will be completed for subjects who are enrolled and receive KTE-X19, at the time points outlined in the SOA:

- Physical exam

- EQ-5D (Phase 2 subjects only; see Section 7.4)
- Disease assessment (see Section 7.7 and Section 7.9)
  - Note: Disease assessment is performed per the SOA through month 24 or until disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then after Month 24 disease assessments will be performed per standard of care.
- Survival Status – subjects may be contacted by telephone to confirm survival status
- Labs (see Section 7.8)
  - CBC with differential
  - Anti-KTE-X19 antibodies
    - For serum samples that demonstrate increased anti-KTE-X19 antibodies at the month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first
  - Blood draw for PBMCs
    - A PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy
- Targeted Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Targeted Concomitant medication documentation (see Section 6.7)
- Subsequent therapy for the treatment of ALL (see Section 6.8)

Subjects who undergo an allogeneic SCT will continue to be followed in the LTFU period and undergo the following assessments at the timepoints outlined in the SOA:

- Disease status
- Survival status
- Serious Adverse Event reporting (see Section 9.4)
- Concomitant medications documentation (see Section 6.7)
- Subsequent therapy for ALL (see Section 6.9)

- Blood draw for:
  - PBMCs
  - If applicable anti-KTE-X19 antibodies (see Section 7.11.9)

Subjects who receive infusion of KTE-X19, but who experience disease progression, will be followed in the LTFU period and undergo the following assessments at the timepoints outlined in the SOA:

- Survival status
- Serious Adverse Event reporting (see Section 9)
- Concomitant medications documentation (see Section 6.7)
- Subsequent therapy for ALL (see Section 6.9)
- Blood draw for:
  - PBMC's
  - If applicable anti-KTE-X19 antibodies (see Section 7.11.9).

Subjects who are enrolled/leukapheresed, but did not receive KTE-X19 treatment, will be followed and will undergo the following assessments at the timepoints outlined in the SOA only until the end of this study (refer to Section 3.5.2):

- Disease assessment per standard of care
- Survival status
- Subsequent therapy for the treatment of ALL (see Section 6.9)
- Adverse/Serious Adverse Event reporting (refer to Section 9)
- Concurrent therapies (see Section 6.7)

Should the subject fail to return to the clinic for a scheduled protocol-specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact the subject will be considered lost to follow-up and no additional contact will be required.

Table 4. Schedule of Assessments

Schedule of Assessments (1 of 2) Procedures	Screening [9]	Enrollment / Leukapheresis	Bridging Chemotherapy	CSF Prophylaxis	Conditioning Chemotherapy Period				IP Administration Period [11]		Post Treatment Follow-up [10, 11] (each visit calculated from Day 0)			
Visit Frequency	**≤ 14 days before enrollment**	**≤ ~5 days after eligibility confirmation**	**Bridging Chemotherapy**	**CSF Prophylaxis**	**-4**	**-3**	**-2**	**-1**	**0**	**1 – 7 [13]**	**Day 14 (± 2 days)**	**Day 28 (+ 3 days)**	**Week 8 (± 1 week)**	**Month 3 (± 2 weeks)**
Medical history	X													
Physical exam	X										X	X	X	X
Vital signs [1]	X [1]	X [5]	X [7]	X [7]	X	X	X		X [1]	X [1]	X	X	X	X
Weight	X	X [5]												
ECOG Performance Status	X				X				X					
Neurological Assessment [8]	X								X	X [8]		X		X
EQ-5D (Phase 2 subjects only) [14]	X								**X**			X		X
ECG	X[9]													
LVEF and PE assessment by ECHO	X[9]													
Chest x-ray	X													
Bone Marrow Evaluation (biopsy and aspirate) for Disease Assessment [2]	X [2]				X [2]					Opt. Day 7 Bx & A [2]		X [2]	X [2]	X [2]
Extramedullary Imaging [3]	X [3]											X [3]	X [3]	X [3]
Overall Response Assessment (Appendix 1)												X	X	X
Leukapheresis [5]		X												
CSF Prophylaxis [6]	X [6]													
Bridging Chemotherapy [6]		X [6]												
Conditioning Chemotherapy (Fludarabine & Cyclophosphamide) [6]					X	X	X							

Schedule of Assessments (1 of 2) Procedures	Screening [9]	Enrollment / Leukapheresis			Conditioning Chemotherapy Period				IP Administration Period [11]		Post Treatment Follow-up [10, 11] (each visit calculated from Day 0)			
Visit Frequency	≤ 14 days before enrollment	≤ ~5 days after eligibility confirmation	Bridging Chemotherapy	CSF Prophylaxis	-4	-3	-2	-1	0	1 – 7 [13]	Day 14 (± 2 days)	Day 28 (+ 3 days)	Week 8 (± 1 week)	Month 3 (± 2 weeks)
KTE-X19 infusion IV									X[12]					
Pregnancy test (serum or urine β-HCG)	X				X									X
Chemistry panel & CBC with differential [7]	X	X [5]	X [7]	X [7]	X	X	X		X	X	X	X	X	X
CD3 count		X [5]												
CD19 immunophenotyping	X [9]													
C-Reactive Protein		X [5]												
Lumbar Puncture for collection of CSF[4]	X [4]			X [4]					X [4]			X [4]		
Anti-KTE-X19 antibody		X [5]										X		X
Peripheral blood	X [7]			X [7]										
Blood draw for PBMCs [11]		X [5]			X [6]					Day 7	X	X	X	X
Blood draw for cytokines [11]		X [5]			X [6]				X	Day 3 and 7	X	X		
Adverse events/ Concomitant medication	X	→												

Footnotes for Schedule of Assessments (1 of 2)

1 Vital signs: Includes blood pressure, heart rate, oxygen saturation, and temperature. Height will be collected at screening. Vitals will be monitored before and after the KTE-X19 infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3oC or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

2 Bone Marrow Evaluation (biopsy and aspirate) for Disease Assessment (Section 7.9): For screening bone marrow evaluation see section 7.9.1. A bone marrow aspirate will be required at all timepoints per the SOA table above (Subjects that receive an SCT, bone marrow evaluations are not required for the first 100 days post SCT). In addition to the bone marrow aspirate, a bone marrow biopsy is required at Screening, Day -4 and Day 28. The Day -4 bone marrow biopsy is only required for subjects receiving bridging chemotherapy. A bone marrow biopsy at all other timepoints is recommended and should be performed if standard of care. Anytime the bone marrow aspirate is a dry tap, then a bone marrow biopsy is required. Disease status will be evaluated per institutional practices. A portion of the aspirate collected will be submitted to the central lab on the day of collection and analyzed for MRD; see the central laboratory manual for details. CCI [redacted]

3 Extramedullary Imaging (Section 7.9.2): For subjects with known baseline extramedullary disease detected through imaging, baseline images appropriate for the anatomical location and clinical scenario will be performed. For subjects receiving bridging chemotherapy, images will be performed after bridging chemotherapy and before conditioning chemotherapy. For subjects not receiving bridging chemotherapy, images will be performed within 28 days before conditioning chemotherapy. On study images will be performed with the same imaging modality and anatomical location as imaged at baseline. Following KTE-X19 infusion, the first on study images will occur at the first occurrence of leukemia remission based on the bone marrow evaluation. Subsequent images will continue as per the SOA through Month 24 or disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then images will be performed per standard of care until disease progression. For subjects with or without extramedullary disease, images should be performed per standard of care anytime the subject presents with symptoms suggestive of disease progression.

4 Lumbar Puncture (Section 7.7): CSF samples will be analyzed locally for disease assessment and centrally for disease assessment and toxicity evaluation at the following timepoints: 1) Baseline – a CSF result obtained within 30 days before enrollment will be acceptable eligibility determination, 2) at the time of CSF prophylaxis, 3) for subjects with baseline CNS-2 disease, a CSF sample is required at the time of first presumed response based on bone marrow (bone marrow <5%), 4) first onset of grade 2 or greater neurological symptoms or as medically indicated 5) for subjects with a CR, collection and analysis of CSF is required to confirm CR and 6) per institutional standard of care. Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, withdrawal of the CSF sample though the reservoir is acceptable. CSF samples (ie, collected on or after informed consent) will be submitted to the central laboratory.

5 Leukapheresis (Sections 6.2 and 7.11.3): All leukapheresis criteria must be met before leukapheresis commences. Vitals, weight, and laboratory sample draws may be performed the s day of or before leukapheresis, except weight must be collected on day of leukapheresis. All laboratory samples should be drawn before the leukapheresis procedure. For EU sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis (see Section 7.11.1).

6 Chemotherapies: Bridging chemotherapy (Section 6.3) will be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy. CSF prophylaxis (Section 6.4) will be administered any time during screening through 7 days before the KTE-X19 infusion. Subjects who are enrolled with CNS-2 disease at baseline must receive CSF prophylaxis after leukapheresis and at least 7 days prior to KTE-X19, unless otherwise approved by the Kite Medical Monitor. Multiple doses of CSF prophylaxis can be given per investigator discretion in accordance with institutional guidelines, but at least 7 days must pass between the last dose of CSF prophylaxis and KTE-X19. Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, administration of CSF prophylaxis through the reservoir is acceptable. Conditioning chemotherapy (Section 6.5) consisting of fludarabine on Day -4, -3, -2 prior to KTE-X19 and cyclophosphamide on Day -2 prior to KTE-X19 will be administered.

7 Vitals, Chem panel, and CBC: collected each day prior to CSF prophylaxis and bridging chemotherapy (see Section 7.11.4 and 7.11.5). CBC 5-part preferred, but 3-part will be acceptable. Peripheral blood: Peripheral blood will be collected at screening, and if the subject did not have bridging therapy than peripheral blood will be collected during day -4 and submitted to the central lab.

8 Neurological assessment: Subjects neurological status should be evaluated at screening to establish a baseline. After enrollment, subjects should be evaluated for any neurological symptoms at each of the timepoints specified in the SOA. During the hospitalization period, evaluations of neurological status may need to be increased.

9 Screening procedures (Section 7.11.1): Procedures should be performed within 14 days of enrollment (unless otherwise specified). ECG: must be performed within 30 days prior to enrollment; ECHO: If the last chemotherapy regimen the subject received is not considered cardiotoxic, then an ECHO performed within 28 days prior to signing the consent may be used for eligibility. If the last chemotherapy regimen the subject received is considered cardiotoxic, then an ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility. CD19: Local CD19 immunophenotyping will be performed at screening on peripheral blood or bone marrow aspirate. Surface CD19 expression should be measured by flow cytometry; IHC analysis is allowed if the bone marrow aspirate is a dry tap, inadequate or there were insufficient circulating blasts for flow cytometry. Procedures that are part of SOC are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility provided they are performed within the time allowance as outlined in the SOA.

10 If the subject progressions before Month 3: Refer to section 7.11.8 for the procedures that are to be completed.

11 Following the initial hospitalization for the KTE-X19 infusion (Section 7.11.8): Following the initial hospitalization for the KTE-X19 infusion, if the subject is hospitalized with any KTE-X19 related adverse event, a blood sample for PBMCs and cytokines will be collected on day of admission, then weekly, and on day of discharge. A PBMC sample should be collected at time of progression and prior to starting subsequent anticancer therapy. As applicable, an additional cytokine sample should be drawn at the first onset and first reoccurrence of any > grade 2 CRS (per Lee 2014 criteria) if not already collected on that day.

12 KTE-X19 pre-medications: Subjects will receive acetaminophen and diphenhydramine (equivalent) approximately 1 hour prior to KTE-X19 (see Section 7.11.7.3).

13 Please refer to Appendix 3 for requirements by country regulatory agencies

14 EQ-5D: The EQ-5D will be completed prior to other study related procedures or assessments.

Schedule of Assessments (2 of 2) Procedures	**Long Term Follow-up Period [8, 9] (Each visit calculated from Day 0)**												
Visit Frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Up to 15 Years**
Physical exam	X	X	X	X	X	X							
EQ-5D (Phase 2 subjects only)	**X**	**X**	**X**	**X**	**X**	**X**							
Bone Marrow Evaluation (biopsy and aspirate) for Disease assessment [1]	X	X	X	X	X	X							
Extramedullary Imaging [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]							
Overall Response Assessment (Appendix 1)	X	X	X	X	X	X							
Survival Status [4, 7, 8]	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential (5 part preferred, 3 part acceptable)	X	X	X	X	X	X							
Anti-KTE-X19 antibody [3, 8]													
Blood draw for PBMCs [8]	X	X	X	X	X	X		X		X		X	X
Adverse Event Reporting [4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Reporting [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for ALL [6, 8]	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Bone Marrow Evaluation (biopsy and aspirate) for Disease Assessment (Section 7.9.1): A bone marrow biopsy and aspirate will be performed per the SOA through Month 24 or until disease progression, whichever occurs first. Disease status will be evaluated per institutional practices. The slides used for the local evaluation of % blasts should be submitted to the central laboratory along with the corresponding pathology report. If the subject's disease has not progressed by Month 24, then after Month 24 bone marrow evaluation will be performed per SOC.

2 Extramedullary Imaging (Section 7.9.2): For subjects with baseline extramedullary disease: Following KTE-X19 infusion, the first on study images will occur at the first occurrence of leukemia remission based on the bone marrow evaluation. Subsequent images will continue as per the SOA through Month 24 or disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then images will be performed per standard of care until disease progression. For subjects with or without extramedullary disease, images should be performed per SOC anytime the subject presents with symptoms suggestive of disease progression.

3 Anti-KTE-X19: For antibody sample collection in long-term follow-up, refer to Section 7.11.9 for details.

4 AE/SAE reporting (Sections 9.2 and 9.4): AEs: After 3 months, only targeted adverse events will be reported in the CRF through 24 months after KTE-X19 infusion or disease progression, whichever occurs first. SAEs: After 3 months, only targeted serious adverse events (including targeted grade 5 serious adverse events) will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. Targeted adverse events include central neurological, hematological, infections, GVHD, autoimmune disorders, and secondary malignancies. Subjects who receive an allogeneic SCT will only be followed for KTE-X19 related serious adverse events. Reporting of these SAEs will commence at the time the SCT preparative regimen commences through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. In addition to the above SAE reporting requirements, anytime a KTE-X19 related serious adverse event occurs it will be reported within 24 hours using the SAE Report Form and in the CRF. All deaths that occur from ICF through end of study will be reported in the CRF.

5 Concomitant medications reporting (Section 6.7): After 3 months of follow-up, only targeted concomitant medications will be collected for 24 months after KTE-X19 infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.
6 Subsequent therapy for ALL (Section 6.9): Documentation of subsequent therapy for ALL will continue to be documented while the subject remains on study. Subjects may be contacted by telephone.
7 Survival Status (Section 7.11.9): Subjects may be contacted by telephone to confirm survival status.
8 If the subject progresses in the LTFU phase (Section 7.11.9), the subject will be followed in the LTFU phase for survival status, subsequent therapy for ALL and have blood drawn for PBMC's and if applicable anti-KTE-X19 antibodies. A PBMC sample should be collected at the time of progression and prior to starting subsequent anticancer therapy.
9 After completion of at least 24 months of assessments in the KTE-C19-103 study, subjects who received an infusion of KTE-X19 will be provided an opportunity to transition to the LTFU study (KT-US-982-5968) after providing signed informed consent, to complete the remainder of the 15-year LTFU period.

8. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product, study treatment or other protocol required therapies and must discuss options for continued participation, completion of procedures and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdraw of full consent for a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdraw of consent will be retained and included in the analysis of the study, and where permitted by local regulations, publically available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole or at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol required investigational products or procedures include any of the following:

- Adverse Event
- Subject request
- Product not available
- Lost to Follow-up
- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9. SAFETY REPORTING

9.1. Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches or blood pressure is now more increased in a subject with pre-existing hypertension). A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered adverse events. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered adverse events.

The term "disease progression" or any relapse after a remission should not be reported as adverse events. Death due to disease progression in the absence of signs and symptoms of underlying disease should be reported as the primary tumor type (eg, B-cell type acute leukemia).

For situations when an adverse event or serious adverse event is due to the disease under investigation report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as adverse events in the appropriate section of the CRF.

The investigators clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol required therapies or the study due to an adverse event, the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.1.1. Diagnosis Versus Signs and Symptoms

For adverse events, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the AE form. The exception is for CRS where both the diagnosis and signs and symptoms will be captured on the CRF AE form. For signs and symptoms of the underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

9.1.2. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an adverse event. A vital sign result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding if an isolated vital sign abnormality should be classified as an adverse event. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the CRF.

9.1.3. Reporting Abnormal Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Associated with clinical symptoms
- Results in a medical intervention (eg, potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

9.2. Reporting of Adverse Events

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject as follows in Table 5:

Table 5. Reporting Requirements for Adverse Events

Subjects who are enrolled, but do not receive KTE-X19 infusion	Subjects who are enrolled and receive KTE-X19 infusion
• Adverse events that occur from enrollment (ie, commencement of leukapheresis) through 30 days after the last study specific procedure (eg, leukapheresis, bridging chemotherapy, conditioning chemotherapy) or until initiation of a new anti-cancer therapy, whichever occurs first, will be reported	• AEs that occur from enrollment (ie, commencement of leukapheresis through 3 months after treatment with KTE-X19 infusion will be reported • After 3 months, only targeted AEs will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, will be reported ○ Targeted adverse events include central neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. • Subjects who receive an allogeneic SCT will only be followed for KTE-X19-related SAEs.

Abbreviations: GVHD, graft-versus-host-disease.
See Section 9.5 for reporting requirements.
See Section 6.7 for targeted concomitant medications and Section 9.5 for targeted SAEs reporting requirements.
See Section 9.5 for reporting requirement for non-serious CRS events Grade ≥ 3.

The investigator must address the below AEs:

- Adverse event diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, chemotherapy or study procedures
- Action taken

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov). Cytokine Release Syndrome events will also be reported using the grading scale outlined in the KTE-X19 IB.

In reviewing adverse events, investigators must assess whether the adverse event is possibly related to 1) leukapheresis, 2) bridging chemotherapy, 3) CSF prophylaxis, 4) Conditioning chemotherapy, 5) the investigational product (KTE-X19), or any protocol required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the adverse event. Additional relevant data with respect to describing the adverse event will be collected in the CRFs.

The investigator is expected to follow reported adverse events until stabilization or resolution. If a subject begins a new anti-cancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.

9.3. Definition of Serious Adverse Events

A SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization
  - An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility (eg, overnight stay).
  - Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization.
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event
  - If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."
- The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each adverse event recorded on the CRF.
- Progression of the malignancy during the study should not be reported as a AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and indicated as being due to disease progression in the CRF. If the malignancy has a fatal outcome before the end of the SAE reporting period, the event leading to the death must be recorded as an SAE with the outcome of being fatal.

9.3.1. Hospitalization and Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE as described in Section 9.5.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative care or hospice care
- Planned hospitalization required by the protocol (eg, for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying cancer

9.4. Reporting Deaths

Death must be reported if it occurs during the SAE reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of KTE-X19 infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the SAE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment.

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of underlying leukemia should be recorded as SAEs with the preferred term “chronic lymphocytic leukemia” and must be reported immediately to the sponsor.

Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. Every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy).

9.5. Reporting of Serious Adverse Events

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject. Unless otherwise indicated in Table 6 below, all SAEs will be reported within 24 hours and recorded in the CRF.

Table 6. Reporting Requirements for Serious Adverse Events

Subjects who are screen-fails or who are enrolled, but do not receive KITE-X19 infusion	Subjects who are enrolled and receive KITE-X19 infusion
• SAEs that occur from signing of the latest informed consent form through 30 days after the last study specific procedure (eg, screening procedure, leukapheresis, bridging therapy, conditioning chemotherapy) or until initiation of a new anti-cancer therapy, whichever occurs first, will be recorded in the CRF	• All SAEs that occur from signing of the screening informed consent form through 3 months after the KITE-X19 infusion or until initiation of another anti-cancer therapy, whichever occurs first • After 3 months, only targeted SAEs will be reported through 24 months after KITE-X19 infusion or disease progression, whichever occurs first o Targeted adverse events include central neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. • Subjects who receive an allogeneic SCT will only be followed for KTE-X19 related SAEs. Reporting of these SAEs will commence at the time the SCT preparative regimen commences through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. • All SAEs deemed related to KITE-X19 infusion regardless of time period • All deaths that occur from signing of the ICF through the end of study will be recorded in the CRF

Abbreviations: SAE, serious adverse event; GVHD, graft-versus-host-disease; CRF, case report form; ICF, informed consent form.
See Section 6.8 for concomitant medication and Section 9.2 for targeted AE reporting requirements.

Following completion of KTE-C19-103, any relevant information on ongoing SAEs must be submitted to Kite Patient Safety and Pharmacovigilance within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via email to the SAE Reporting mailbox: safety_FC@gilead.com

Subsequently, all SAEs will be reported to the health authorities per local reporting guidelines.

9.6. Pregnancy and Lactation

There is no relevant clinical experience with KTE-X19 in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 6 months after conditioning chemotherapy dosing or the administration of KTE-X19, whichever is longer. Male subjects are recommended to not father a child for 6 months after the conditioning chemotherapy dosing or the administration of KTE-X19, whichever is longer.

Any pregnancy in a female subject enrolled in the study must be reported, regardless of the time after the KTE-X19 infusion. If pregnancy occurs in a female partner of a male subject within 6 months after completing conditioning chemotherapy or the KTE-X19 infusion, whichever is longer, the pregnancy must be reported. All such pregnancies must be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Report Form within 24 hours after becoming aware of the pregnancy. Information regarding the pregnancy and/or the outcome will be requested by Kite. Pregnancy Report Forms should be reported to Kite Patient Safety and Pharmacovigilance via email: Safety_FC@gilead.com or fax: +1 (650) 522-5477.

The pregnancy itself or an induced elective abortion to terminate a pregnancy without medical reasons are not considered AEs. Any premature termination of a pregnancy (eg, spontaneous abortion, induced therapeutic abortion due to complications, or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. Any SAE occurring as an adverse pregnancy outcome after the study has been completed must be reported to Kite Patient Safety and Pharmacovigilance.

The pregnant subject or subject partner should receive appropriate monitoring and care until conclusion of the pregnancy. The outcome should be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Outcome Report Form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Patient Safety and Pharmacovigilance.

If a lactation case occurs in a female subject in the study, the lactation case must be reported to Kite Patient Safety and Pharmacovigilance within 24 hours after the investigator's awareness of the event using the Special Situations Reporting Form. In addition to reporting a lactation case during the study, investigators should monitor for pregnancy and lactation cases throughout the LTFU period. Report the lactation case and Special Situations Reporting Forms to Kite Patient Safety and Pharmacovigilance via email: Safety_FC@gilead.com or fax: +1 (650) 522-5477.

9.7. Safety Review Team and Dose-limiting Toxicity

The SRT, that is internal to the study sponsor and in collaboration with at least one study investigator, will be specifically chartered to review safety data from the first 3-12 subjects treated with KTE-X19 and make recommendations on further study conduct and progression of the study based on the incidence of KTE-X19 DLT and review of serious adverse events.

Dose-limiting toxicity is defined as the following KTE-X19-related events with onset within the first 28 days following KTE-X19 infusion:

- Grade 4 hematologic toxicity lasting more than 30 days (except lymphopenia) if not attributable to underlying disease

- All KTE-X19-related grade 3 non-hematologic toxicities lasting for > 7 days and all KTE-X19-related grade 4 non-hematologic toxicities regardless of duration are considered DLTs, with the exception of the following which are not considered DLTs:

- Aphasia/dysphasia or confusion/cognitive disturbance which resolves to at least grade 1 or baseline within 2 weeks and to at least baseline within 4 weeks.
- Fever grade 3 or 4
- Immediate hypersensitivity reactions occurring within 2 hours of KTE-X19 infusion (related to KTE-X19 infusion) that are reversible to a grade 2 or less within 24 hours of KTE-X19 infusion with standard therapy
- Renal toxicity which requires dialysis for ≤ 7 days
- Intubation for airway protection if ≤ 7 days
- Tumor lysis syndrome (TLS) including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, hyperuricemia)
- Grade 3 transaminase, alkaline phosphatase, bilirubin or other liver function test elevation, provided there is resolution to ≤ grade 2 within 14 days
- Grade 4 transient serum hepatic enzyme abnormalities provided there is resolution to ≤ grade 3 within < 72 hours
- Hypogammaglobulinemia grade 3 or 4
- Grade 3 nausea and/or anorexia

CRS will be graded according to a revised grading system {Lee 2014}. Adverse events attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT. Consistent with non-CRS toxicities, all occurrences of grade 3 CRS of duration > 7 days and all occurrences of grade 4 CRS are considered DLTs, other than occurrences of CRS due to the exceptions listed above.

Three subjects will initially be enrolled to evaluate the safety of the KTE-X19 regimen. Subjects will be evaluated for DLTs within the first 28 days following the completion of the KTE-X19 infusion. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.5. The SRT will make recommendations based on the incidence of DLT and overall safety profile of the KTE-X19 regimen as outlined below**:**

- If the subject incidence of DLT is 0 of 3 subjects, the SRT may recommend either
  - proceeding to Phase 2 at 2 x 10^6 anti-CD19 CAR T cells/kg; or
  - accrual of additional subjects in Phase 1 to further characterize risk/benefit prior to Phase 2
- If the subject incidence of DLT is 1 of 3 subjects, the SRT may recommend either

— accrual of an additional 3 subjects at the same cell dose with re-evaluation of the incidence of DLT after a total of 6 subjects in the DLT evaluable set have been assessed for DLT. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT in the 6 subjects is ≤ 1 of 6 subjects; or

— evaluation of a lower dose of 1 x 10^6 anti-CD19 CAR T cells/kg in an additional set of 3-6 subjects. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT is < 33%.

- If the subject incidence of DLT is ≥ 2 of 3 subjects, a lower dose of 1 x 10^6 anti-CD19 CAR T cells/kg in an additional set of 3-6 subjects will be explored. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT is < 33%.

If the conditioning chemotherapy regimen and KTE-X19 dose evaluated in Phase 1 is determined to be safe based on the incidence of DLT, up to approximately 40 additional subjects (high and non-high burden disease) may be enrolled at 2 x 10^6 anti-CD19 CAR T cells/kg, 1 x 10^6 anti-CD19 CAR T cells/kg, or 0.5 x 10^6 anti-CD19 CAR T cells/kg prior to commencing Phase 2. The data from these additional subjects will be reviewed by the SRT who will provide recommendations for dose for Phase 2. Further details to be outlined in the SRT Charter.

Based on the review of all available safety and efficacy data, the benefit/risk ratio was considered most favorable at the dose of 1 x 10^6 anti-CD19 CAR T cells/kg, therefore the dose of 1 x 10^6 anti-CD19 CAR T cells/kg was considered the recommended Phase 2 dose.

The final decision to commence Phase 2 and the dose selected for Phase 2 was formally communicated to participating sites in a separate communication.

9.8. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be chartered to review safety data to make trial conduct recommendations. The DSMB will review safety data in an interim analysis during the Phase 2 portion of the study. For this interim analysis, the DSMB will review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion. During Phase 2, Kite Pharma or delegate will submit SAEs or suspected unexpected serious adverse reactions (SUSARs) to the DSMB chair for risk benefit analysis. The DSMB Chair will review reported SAEs at least monthly and SUSARs as soon as received. .

9.9. Criteria to Pause Enrollment

Study enrollment will be paused in Phase 1 (DLT Evaluation Period) following any grade 5 adverse event that occurs within 30 days of KTE-X19 dosing regardless of attributions. The DLT evaluation period is now complete (see Section 2.8).

As part of its oversight of the study, the DSMB also will assess criteria to pause enrollment in Phase 2 after 10, 20, and 35 subjects enrolled in Phase 2 have been treated with KTE-X19 and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following is met:

Subject incidence of the following grade 4 KTE-X19-related adverse events lasting more than 7 days is >33%:

- Neurologic events
- CRS (per Lee 2014 criteria)
- Other non-hematological serious adverse event
- Infection (treatment-related)

10. STATISTICAL CONSIDERATIONS

CCI [redacted]

[redacted]

[redacted]

10.2. Study Endpoints

10.2.1. Primary

Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT)

Phase 2: Overall complete remission rate (CR + CRi) per independent review (Appendix 1). All subjects that do not meet the criteria for CR or CRi by the analysis data cutoff date will be considered non-responders for the overall complete remission rate evaluation.

10.2.2. Secondary

- Duration of Remission (DOR): for subjects who experience CR or CRi per independent review, DOR is defined as the time between their first complete response per indepedent review to relapse or any death in the absence of documented relapse. Relapse is defined in Appendix 1. Subjects who do not meet the criteria for relapse and who have not died will be censored at the last evaluable disease assessment or disease status follow up assessment. A sensitivity analysis will be conducted in which non-disease mortality will be considered a competing risk. Disease assessments obtained after new anti-cancer therapies (including allogeneic SCT) will not contribute to the derivation of duration of remission. The DOR for subjects that undergo allogeneic SCT while in remission is censored at the date of the allogeneic SCT; the DOR for subjects that undergo other new anti-cancer therapies in the absence of documented relapse is censored at the last evaluable disease assessment prior to the new anti-cancer therapies.

- In subjects who achieve CR, a TKI may be resumed 2 months after KTE-X19 infusion. In such subjects who resume TKI therapy, disease assessments obtained after resumption of TKI therapy will contribute to the derivation of the duration of remission. A sensitivity analysis will be conducted in which the duration of remission in such subjects is censored at the first date of the resumption of TKI therapy.

- Minimum Residual Disease (MRD) Negative Rate: The incidence of a minimal residual disease response (MRD-). MRD- is defined as MRD < 10^{-4} per the standard assessment (see Section 7.10).
- Overall complete remission rate (CR + CRi) per investigator assessment (Appendix 1).
- Allogeneic Stem Cell Transplant (Allogeneic SCT) Rate
- Overall Survival: OS is defined as the time from KTE-X19 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.
- Relapse-free Survival (RFS): RFS is defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause. Subjects not meeting the criteria for relapse by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who have not achieved a complete remission (CR or CRi) at the analysis data cutoff will be evaluated as having an RFS event at Day 0.
- Incidence of adverse events and CTCAE grade changes in safety laboratory values.
- Incidence of anti-KTE-X19 antibodies.
- Changes over time in the EQ-5D scale score and EQ-5D VAS score

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[redacted]

10.2.4. Covariates

The primary endpoints and selected secondary endpoints will be evaluated in subgroup analysis by subjects with or without prior blinatumomab, and by subjects with or without prior inotuzumab. Such subgroup analyses may not be performed if too few (eg, $n < 5$) subjects in the mITT set have received prior blinatumomab or prior inotuzumab at the time of the analysis.

Additional covariates and subgroup analyses will be outlined in the Statistical Analysis Plan.

10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 100 subjects.

The primary efficacy endpoint and all analyses based on the response will be based on a mITT population consisting of all subjects who receive any dose of KTE-X19 in Phase 2.

This study uses a single-arm design to test for an improvement in overall complete remission rate. For the test of efficacy this study has approximately 93% power to distinguish between an active therapy with a 65% true overall complete remission rate from a therapy with an overall complete remission rate of 40% or less with a 1-sided alpha level of 0.025. A step-down test of the secondary endpoint MRD-negative Rate will be performed against a MRD-negative rate of 30% if the testing of the overall complete remission rate is significant.

In Phase 1, the SRT will review safety data after 3 subjects in the DLT evaluable set (see Section 10.5) have had the opportunity to be followed for 28 days after the KTE-X19 infusion. If the conditioning regimen and KTE-X19 dose evaluated in Phase 1 is determined to be safe based on the incidence of DLT, up to approximately 30 additional subjects may be enrolled to further evaluate safety prior to commencing Phase 2.

During Phase 2, one interim and one primary analyses will be performed. The interim analysis is for safety only and will occur after 20 subjects have been treated with KTE-X19 and have had the opportunity to be followed for 30 days after the KTE-X19 infusion. The primary analysis will occur when the overall study enrollment is complete and all subject in the mITT set have had the opportunity to complete the month 6 disease assessment. 65% Approximately 100 subjects may be enrolled into the entire study. At the time of the primary analysis, in the event that either less than or more than 50 subjects are eligible for the mITT set, all mITT eligible subjects will be included in the analysis.

10.4. Statistical Assumptions

This study assumes that the underlying overall complete remission rate (in the absence of treatment with investigational therapy) is 40%. For MRD- rate, it is assumed that the underlying response rate (in the absence of treatment with investigational therapy) is 30%.

10.5. Analysis Subsets

KTE-X19 will be administered as a single infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg or 1×10^6 anti-CD19 CAR T cells/kg or 0.5×10^6 anti-CD19 CAR T cells/kg . For subjects weighing greater than 100 kg, a maximum flat dose of 2×10^8 or 1×10^8 or 0.5×10^8 anti-CD19 CAR T cells/kg may be administered. Full Analysis Set: the full analysis set will consist of all enrolled subjects and will be used for summaries of subject disposition.

Modified Intention-to-treat Set (mITT): the modified intention-to-treat set will consist of all subjects enrolled in Phase 2 and treated with KTE-X19. The mITT analysis set will be used for all efficacy analyses unless otherwise specified.

DLT-evaluable set: All Phase 1 subjects treated with the target KTE-X19 dose and followed for at least 28 days, or received a dose of KTE-X19 lower than the target dose but experienced a DLT during the 28 day post infusion period, up to the time at which a dose level has been evaluated for DLT and deemed safe. Additional Phase 1 subjects enrolled and treated subsequently for the purpose of assessment of the overall safety in the same dose level or a lower dose level will not be considered as part of the DLT evaluable set, and DLT will not be assessed for such subjects.

Safety analysis set: the safety set is defined as all subjects treated with any dose of KTE-X19.

10.6. Access to Individual Subject Treatment Assignments

This is a single arm, open-label study and subjects and investigators will be aware of treatment received. Data handling procedures will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan, DSMB charter, and Trial Integrity Document.

10.7. Interim Analysis

During Phase 1, the SRT will review safety data after 3 DLT evaluable subjects have had the opportunity to be followed for 28 days after the KTE-X19 infusion. The SRT will review the safety data and make recommendations on further study conduct and progression of the study as outlined in Section 9.6.

During Phase 2, the DSMB will review safety data after 20 Phase 2 subjects have been treated and followed for 30 days. The DSMB will also review SAEs on a monthly basis prior to the primary analysis. The DSMB may request additional safety data or modifying the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may not have undergone completion of data cleaning procedures in order to facilitate timelines for DSMB review.

10.8. Planned Method of Analysis

The primary efficacy analysis will be performed when all subject in the mITT set have had the opportunity to complete the month 6 disease assessment. Additional analyses may occur after the primary analysis has been completed. These additional analyses will be descriptive and will occur after inferential testing has been performed. The final analysis will occur when all subjects have completed the study.

10.8.1. Overall Complete Remission Rate

The incidence of response and exact 2-sided 95% confidence intervals will be generated. An exact binomial test will be used to compare the observed response rate to a response rate of 40%.

10.8.2. Duration of Remission

Duration of Remission (DOR): for subjects who experience CR or CRi per independent review, DOR is defined as the time between their first complete response per independent review to relapse or any death in the absence of documented relapse. Relapse is defined in Appendix 1. Subjects who do not meet the criteria for relapse and who have not died will be censored at the last evaluable disease assessment or disease status follow up assessment. Disease assessments obtained after new anti-cancer therapies (including allogeneic SCT) will not contribute to the derivation of duration of remission. The DOR for subjects that undergo allogeneic SCT while in remission is censored at the date of the allogeneic SCT; the DOR for subjects that undergo other new anti-cancer therapies in the absence of relapse is censored at the last evaluable disease assessment prior to the new anti-cancer therapies. Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for DOR. Estimates of the proportion of subjects remained as in complete remission at 3-month intervals will be provided.

A sensitivity analysis of DOR will be conducted in which non-disease mortality will be considered a competing risk. A competing-risk analysis method {Klein 2005, Putter 2007} will be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence non-disease related mortality (the competing risk) will be estimated along with 2-sided 95% confidence intervals at 3-monthly time intervals.

10.8.3. MRD-negative rate

The incidence of MRD-negative rate and exact 2-sided 95% confidence intervals will be generated. If the statistical testing of the primary endpoint (overall complete remission rate) is significant, an exact binomial test will be used to compare the observed MRD-negative rate to a rate of 30% at a one-sided alpha level of 0.025.

10.8.4. CR Rate, CRi Rate, and DOR to Treatment Among Subjects Retreated with KTE-X19 for Progressive Disease after Initial Remission

The incidence of CR rate, and CRi rate, and exact 2-sided 95% confidence intervals will be generated.

DOR to retreatment is defined only for subjects who experience a CR or CRi to retreatment and is the time from the first complete remission after retreatment to relapse after retreatment or death due to disease relapse. The competing-risk analysis method will be used to estimate the cumulative incidence of relapse after retreatment.

10.8.5. Overall Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

10.8.6. Allogeneic Stem Cell Transplant Rate

The incidence of Allogeneic SCT in the mITT set and 2-sided 95% confidence intervals will be generated.

10.8.7. Safety

Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4.03 grade 3 or higher and treatment related AEs reported throughout the conduct of the study will be tabulated by preferred term and/or system organ class. CTCAE grade changes in safety laboratory values will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths and treatment related SAEs will be provided.

10.8.8. Long-term Data Analysis

All subjects will be followed for survival status for up to 15 years after receiving KTE-X19. LTFU data analysis will be performed on subjects in this study and after transition to the KT-US-982-5968 LTFU study. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

11. REGULATORY OBLIGATIONS

11.1. Independent Review Board /Independent Ethics Committee

A copy of the protocol, ICF and any additional subject or trial information such as subject recruitment materials must be submitted to each sites respective IRB/IEC for approval. Once approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site specific and study serious adverse events (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2. Subject Confidentiality

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number
- Date of birth or year of birth/age at time of enrollment will be reported according with local laws and regulations

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth (as per their local reporting requirements for both initials and date of birth)

Per federal regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, CRO, IRB/IEC and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records which includes personal information.

11.3. Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the investigators agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact.

Both Kite Pharma and the investigator reserve the right to terminate the investigators participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at is sole discretion, to determine whether to manufacture KTE-X19 T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralize filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject identification lists
- Protocols and protocol amendments, investigator brochure, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records and experimental product related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility (ies), review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of CRFs, refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in study KTE-C19-103 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on
  - — Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work AND
  - — Drafting the article or revising it critically for important intellectual content; AND
  - — Final approval of the version to be published; AND
  - — Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma for review and approval. The study contract between the institution, principal investigation and Kite Pharma or its delegate will outline the requirements for publication review.

16. COMPENSATION

Kite Pharma will provide compensation for study related illness or injury pursuant to the information outlined in the injury section of the ICF.

17. REFERENCES

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18. APPENDICES

Appendix 1. OVERALL DISEASE RESPONSE CLASSIFICATION

Response	BM		Peripheral Blood [d]		CNS EMD		Non-CNS EMD [b, e]
CR	≤ 5% [f]	*and*	ANC ≥ 1,000 and Plt ≥ 100,000	*and*	CNS-1	*and*	CR [c]
CRi			ANC ≥ 1000 and Plt < 100,000 OR ANC < 1000 and Plt ≥ 100,000				
CRh			ANC ≥ 500 and Plt ≥ 50,000 but not CR				
Blast-free hypoplastic or aplastic BM			Any values not meeting criteria for CR, CRi or CRh				
PR	All criteria for CR, CRi, CRh or blast-free hypoplastic or aplastic bone marrow are met					*and*	PR
Relapse	>5% [f]	*or*	Circulating leukemia present [a]	*or*	CNS-2 or CNS-3	*or*	PD
No response	All required assessments are performed with failure to attain the criteria needed for any response category						
Unknown	Assessment is not done, incomplete, or indeterminate Note: Overall disease response can be assessed as 'Relapsed disease' if any single element of disease response assessment shows relapse, other Unknown elements of disease response assessment do not need to be evaluated						

ANC = absolute neutrophil count; BM = bone marrow; EMD = extramedullary disease; Plt = platelets;

a No circulating leukemia is < 1% circulating blasts by morphology; Circulating leukemia is ≥ 1% circulating blasts by morphology; If ≥ 1% blast by morphology and there is no other evidence of leukemia, then flow or molecular studies should be conducted to confirm that blasts are leukemia.

b See Overall Non-CNS EMD table (Appendix 2)

c If baseline EMD is present, then images must show CR. If no baseline EMD, then images are not required, but if performed, must show CR per Appendix 2.

d ANC and Plt: The units for Plt and ANC are per uL. ANC and Plt values should be evaluated every time a BM evaluation is performed. If not done, ANC and Plt values used for response assessment can be from any time 7 days prior to the BM result to any time after the BM result.

e In subjects evaluated for non-CNS EMD, imaging and bone marrow results used for assessment of overall disease response must be within 30 days of each other

f Blasts by morphology in BM

Appendix 2. EXTRAMEDULLARY DISEASE RESPONSE

Subjects with known baseline extramedullary disease (EMD) should have disease assessed by the investigator per the Table below at baseline and post-baseline with an imaging modality appropriate for the anatomical site and clinical scenario (eg, MRI for CNS lesion, ultrasound for testicular lesion, CT for intra-abdominal or thoracic lesion) and with the same imaging modality throughout.

Response [a]	PET Baseline, On-study		Baseline lesion(s) (by CT or MRI) [b]		New Lesion(s)

CR	Neg, N/A	*and*	All of:
			• Disappearance of measurable and non-measurable nodal lesions:
			  ○ Nodal masses >1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤1.5 cm in GTD
			  ○ Nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0cm in their short axis after treatment
			• If testes, spleen and/or liver involvement, they must be normal size by imaging or physical examination.
				and	No

	Pos, Neg	*and*	Any	*and*	No
PR	Any	*and*	All of: • ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant masses. Dominant masses should be clearly measurable in at least 2 perpendicular dimensions, and should be from different regions of the body if possible. • No increase in size of liver or spleen by imaging or physical exam • If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for a single nodule.	*and*	No
SD	Does not meet the criteria for CR, PR, or PD				
PD	Any	*and*	At least one of the following: • ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node. • At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis • Greater than or equal to a 50% increase in size of splenic, hepatic or any other non-nodal lesion.	*or*	Yes

Neg = Negative; Pos = Positive; N/A = Not applicable
a Modified Revised IWG Criteria {Cheson 2007}
b see Section 7.9.2 of protocol for details.

Appendix 3. SCHEDULE OF ASSESSMENTS FOR GERMAN SUBJECTS FOLLOWING KTE-X19 INFUSION

The post-infusion monitoring of subjects, described in section 7.11.7.2 in this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in the Schedule of Assessment Table, column "IP administration period, 1-7". The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see section 7.4), blood draw for chemistry panel with CRP, ferritin (and LDH if indicated as per section 7.11.7.4), blood draw for CBC w/differential, and neurological assessment (see section 7.5). Any observed toxicity will be managed according to section 6.10 of this protocol.