CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Protocol Number:	KTE-C19-108 (ZUMA-8)
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Clinical Study Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404
Key Sponsor Contacts:	PPD Sr Medical Director, Clinical Development Phone: PPD email PPD PPD Clinical Program Manager, Clinical Operations Phone: PPD Email PPD
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PROTOCOL SYNOPSIS

Kite Pharma, Inc.
2400 Broadway
Santa Monica, CA 90404

Title:	A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Indication:	Adult subjects with relapsed or refractory (r/r) chronic lymphocytic leukemia (CLL) and r/r small lymphocytic lymphoma (SLL) who have been previously treated with at least two prior lines of therapy, at least one of which must have included any Bruton's tyrosine kinase (BTK) inhibitor
Study Design:	ZUMA-8 is a Phase 1, multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with r/r CLL and SLL. During the study, approximately 15 to 27 subjects with r/r CLL and SLL will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, in collaboration with at least 1 study investigator, will review all data available, including safety and efficacy data and make recommendations regarding further enrollment based on the incidence of dose-limiting toxicities (DLTs) and overall safety profile and cell expansion of KTE-X19. See Section 9.7. The trial will separated into two different stages: In the first stage, subjects with r/r CLL will be enrolled using a 6+3 study design into cohorts described below: • **Cohort 1:** Up to 9 subjects will be enrolled at 1 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 2 will be based on incidence of DLT in Cohort 1. • **Cohort 2**: Up to 9 subjects will be enrolled at 2 x 10^6 anti-CD19 CAR T cells/kg. In the second stage (Amendment 2), subjects with r/r CLL and SLL will be enrolled into Cohort 3 and 4 as described below: • **Cohort 3:** Three (3) subjects with r/r CLL andSLL with ≤ 1% malignant cells in peripheral blood or absolute lymphocyte count (ALC) < 5,000 cells/μL will be enrolled and dosed with KTE-X19 at a dose of 1 x 10^6 anti-CD19 CAR T cells/kg. Subjects must have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor. This is an exploratory cohort. No additional dose levels will be evaluated.

- **Cohort 4**: Up to approximately 15 subjects with r/r CLL who have been previously treated with at least two prior lines of therapy and are receiving ibrutinib as a single agent, or ibrutinib in combination with anti-CD20 antibodies, BCL-2 inhibitors, and PI3k inhibitors as the last line of therapy. Subjects must have received ibrutinib for at least 6 months prior to screening. Ibrutinib administration will continue up to 30 hours prior to leukapheresis. In case of treatment interruption with ibrutinib, the principal investigator should reach out to the medical monitor to discuss. A 3+3 study approach will be used to evaluate two doses of KTE-X19.
  - Cohort 4A:
    - Up to 6 subjects using 3+3 approach will be enrolled and dosed at 1 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 4B will be based on SRT review of Cohort 4A.
  - **Upon completion of Cohort 4A SRT, it was determined not to enroll subjects in Cohort 4B*.
  - Cohort 4B:
    - Up to 12 subjects will be enrolled and dosed at 2 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg.

Once a safe dose is established in Cohort 4, additional subjects will be enrolled and dosed for a total of up to twelve (12) subjects at the safe dose level. The maximum number of subjects enrolled and dosed in Cohort 4 will be approximately 15 subjects.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- [redacted]
- Lymphodepleting/Conditioning chemotherapy
- Investigational product (IP) treatment
- Post-treatment assessment
- Long-term follow-up

For study requirements assigned to each study arm, refer to the schedule of assessments (SOA) and Section 7 for details.

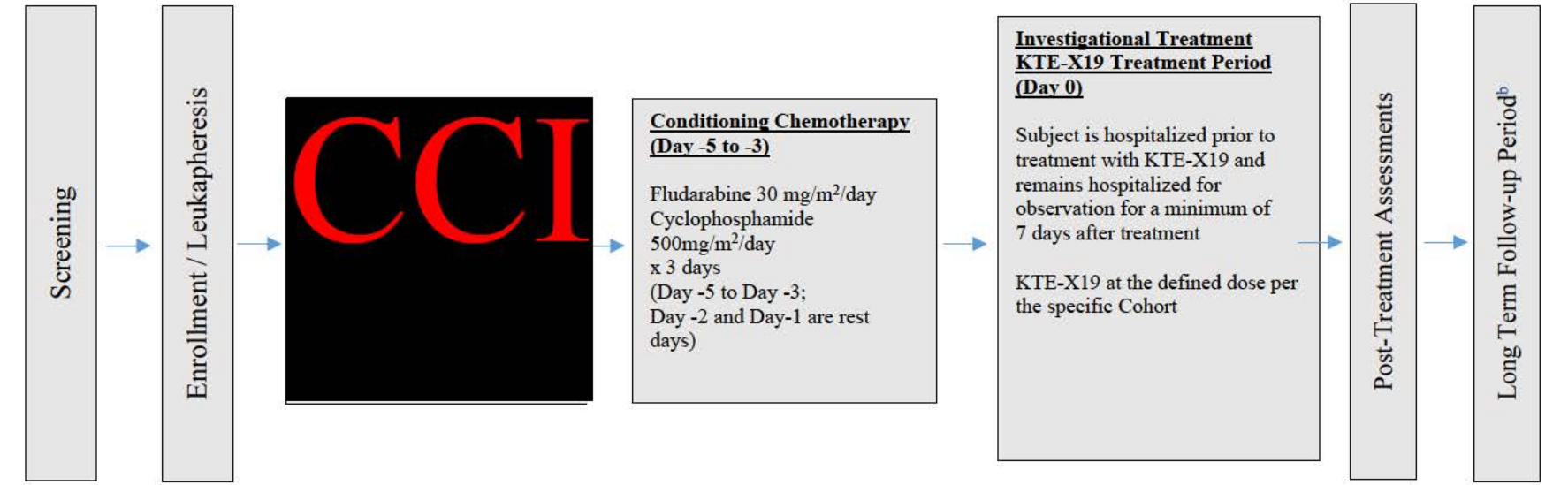
A study schema is provided at the end of the protocol synopsis section.

Study Objectives:	Primary objective of Phase 1: Evaluate the safety and tolerability of KTE-X19 in subjects with r/r CLL and SLL. Secondary objectives are to characterize the safety profile and anti-KTE-X19 antibody, and to evaluate the efficacy of KTE-X19 as measured by the objective response rate (ORR) per investigator review in subjects with r/r CLL treated with KTE-X19. Efficacy analysis for ORR will be performed only for the selected safe dose cohort. CCI [redacted]
Hypothesis:	No formal hypothesis testing for this phase 1 study.
Primary Endpoints:	Incidence of DLTs in subjects treated with KTE-X19 (Section 9.7)
Secondary Endpoint(s):	• ORR (CR/CRi/PR) per investigator review as defined by IWCLL 2018 criteria (Appendix 3) for selected safe dose cohort • Incidence of adverse events (AEs) • Levels of anti-CD19 CAR T cells in blood
Sample Size:	Up to approximately 27 subjects will be enrolled and treated in the study.
Study Eligibility:	See Section 5 for list of all eligibility criteria.
Treatment:	All subjects will receive conditioning chemotherapy followed by the investigational treatment, KTE-X19. CCI [redacted] **Conditioning Chemotherapy** KTE-X19 is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day administered IV over 30 minutes on Day −5, Day −4, and Day −3 prior to KTE-X19 infusion. Day −2 and Day −1 are rest days.

	KTE-X19 KTE-X19 treatment consists of a single infusion of CAR-transduced autologous T cells administered intravenously (IV) at a target dose of 1 x 10^6 or 2 x 10^6 anti-CD19 CAR T cells/kg (Section 3.1). All subjects will be hospitalized to receive KTE-X19 infusion followed by a minimum 7-day observation period. Refer to Section 6.1.4 and Section 7.9.3.2 for treatment details. Refer to Section 6.1.3 and Section 7.9.3 for chemotherapy treatment details.
CCI [redacted]	[redacted]
Procedures:	At specific time points as outlined in the SOA, subjects will undergo the following procedures: collection of informed consent; general medical history, including previous treatments for CLL and SLL; physical exam, including vital signs and Eastern Cooperative Oncology Group (ECOG) performance status; local blood draws for complete blood count (CBC), chemistry panels, lactate dehydrogenase (LDH), C-reactive protein, ferritin; central blood draws for cytokines, lymphocyte subsets, antibodies to anti-CD19 CAR T cells, replication-competent-retrovirus (RCR), and anti-CD19 CAR T cell analysis. Women of childbearing potential will undergo a urine or serum pregnancy test.

	Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO/MUGA), diagnostic computed tomography(CT) scan (preferred) or magnetic resonance imaging (MRI) of the head, neck, chest, abdomen, and pelvis, bone marrow aspirate and biopsy, CCI [redacted] and leukapheresis. Routinely throughout the conduct of the study, all subjects will be asked to report concomitant therapies, AEs, and subsequent CLL andSLL therapy. Subjects will undergo neurological assessment. For details for all study requirements, refer to Section 7 and the SOAs.
Statistical Considerations:	The primary endpoint for the Phase 1 portion of the study is incidence of DLTs in subjects treated with KTE-X19. A 6 + 3 dose escalation/de-escalation plan was used in the Cohort 1 and Cohort 2 DLT evaluation period. Amendment 2 will use a 3 + 3 dose escalation plan for Cohort 4. Cohort 3 is an exploratory cohort. For the selected safe dose cohort, the ORR (CR/CRi/PR) will be calculated for mITT analysis set. A 95% confidence interval will be provided by Clopper-Pearson method. The mITT set is defined as all subjects treated with KTE-X19 and with radiographically measurable disease CCI [redacted] prior to administration of conditioning chemotherapy.

Figure 1. Study Schema



b After the end of KTE-C19-108, 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.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALC	Absolute lymphocyte count
BCL-2	B-cell lymphoma 2
BR	Bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CAR	Chimeric antigen receptor
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRi	Complete response with incomplete hematopoetic recovery
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DLT	Dose-limiting toxicity
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FAS	Full analysis set
FCR	Fludarabine cyclophosphamide, and rituximab
GCP	Good Clinical Practice
GVHD	Graft-versus-host disease
HEENT	Head, ears, eyes, nose, and throat
HLH	Hemophagocytic lymphohistiocytosis
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Hamonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational product
IPM	Investigational Product Manual
IRB/IEC	Institutional Review Board/Endependent Ethics Committee
ITK	IL-2-inducible T-cell kinase
IV	Intravenous

IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KI	Kinase inhibitor
LP	Lumbar puncture
LVEF	Left ventricular ejection fraction
LTFU	Long-term Follow-up
mITT	Modified intend to treat
MRI	Magnetic resonance imaging
MRD	Minimal residual disease
NCI	National Cancer Institute
OS	Overall survival
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PFS	Progression-free survival
PI-3K	Phosphoinositide 3-kinase inhibitor
PK	Pharmacokinetic(s)
PR	Partial response
r/r	Relapsed/refractory
RCR	Replication-competent retrovirus
SAE	Serious adverse event
scFv	Single chain variable fragment
SCT	Stem cell transplant
SLL	Small lymphocytic lymphoma
SOA	Schedule of assessments
SOC	Standard of care
SRT	Safety review team
TEAEs	Treatment emergent adverse events
Tcm	Central memory T cells
Treg	Regulatory T cells
WBC	White blood cell

1. OBJECTIVES

1.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of KTE-X19 in subjects with relapsed or refractory (r/r) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

1.2. Secondary Objectives

Secondary objectives are to characterize the safety profile and anti-KTE-X19 antibodies, and to evaluate the efficacy of KTE-X19 as measured by the objective response rate (ORR) per investigator review in subjects with r/r CLL treated with KTE-X19. Efficacy analysis for ORR will be performed only for the selected safe dose cohort.

CCI [redacted]

[redacted]

2. DISEASE BACKGROUND

2.1. CLL and SLL Disease Background

CLL is the most commonly occurring leukemia in Europe and the United States (US) with an estimated lifetime risk of 1:167 {Sant 2010, Surveillance Epidemiology and End Results (SEER) Program 2011}. CLL is marked by the progressive accumulation of functionally impaired monoclonal B lymphocytes in blood, bone marrow, lymph nodes, spleen, and liver {Hallek 2018, Rozman 1995}. Symptoms include fever, night sweats, and weight loss, and disease progression is often accompanied by lymphadenopathy, splenomegaly, or hepatomegaly. CLL is most commonly a disease of the elderly, as 70% of patients are ≥ 65 years at diagnosis, and the median age is 72 years {Surveillance Epidemiology and End Results (SEER) Program 2011}. Patients harboring a deletion of the short arm of chromosome 17 (del17p) or an inactivating mutation in the TP53 gene (TP53mut) are considered to be high-risk and have worse survival outcomes than patients who do not harbor these mutations {Hallek 2019}.

CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same disease. SLL are the less frequent nonleukemic cases of CLL, where lymph node involvement is prevalent, in the absence of cytopenias caused by a clonal bone marrow infiltrate, and with $< 5 \times 10^9$/L B lymphocytes in the peripheral blood {Tsimberidou 2007}. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with $< 5 \times 10^9$/L B lymphocytes in the peripheral blood. In SLL, the diagnosis should be confirmed by histopathology evaluation of a lymph node biopsy. SLL follows the same management guidelines as CLL {Scarfo 2016}. The indolent clinical behavior of SLL has often led to the approach of deferring treatment in asymptomatic patients until progressive disease (PD) becomes evident.

For the treatment of CLL and SLL, chemoimmunotherapy remains an option, particularly as an initial treatment, for those who are considered to be fit and of favorable-risk. The CLL8 and CLL10 studies of the German CLL group established the benefit of adding an anti-CD20 monoclonal antibody to chemotherapy and the value of the fludarabine, cyclophosphamide, and rituximab (FCR) and bendamustine and rituximab (BR) regimens for the treatment of CLL {Eichhorst 2016, Hallek 2010}. The CLL11 study subsequently demonstrated improved outcomes with the third generation anti-CD20 antibody obinutuzumab in combination with chlorambucil compared with rituximab-chlorambucil and chlorambucil monotherapy {Goede 2014}. For the overwhelming majority of patients, these treatments are not curative; the disease eventually relapses, necessitating further intervention to establish and maintain tumor control. While chemoimmunotherapy can be pursued at the time of relapse, it is associated with toxicity, including myelosuppression and fatigue. Patients who relapse after an initial remission duration ≥ 3 years after frontline FCR are considered suitable to receive FCR again as the first salvage therapy. Salvage treatment offers limited benefit for patients with a limited depth of response to initial therapy or those who have recurrent disease within 3 years {Tam 2014}. Patients with del17p or TP53mut are particularly poorly served by chemoimmunotherapy irrespective of treatment history.

Small molecule targeted agents have transformed the treatment landscape for CLL, largely supplanting chemoimmunotherapy, but these agents require chronic administration. One such agent is ibrutinib, a first-in-class irreversible inhibitor of Bruton's tyrosine kinase (BTK) that is approved for the treatment of both previously untreated and r/r CLL. In the r/r setting, it results in a high objective response rate (ORR) (> 80%) when used in combination with a BR regimen, but a limited depth of response (< 22% CR/CRi) {Chanan-Khan 2016}. Among those who progress on ibrutinib, a significant proportion of patients develop high-risk disease and have poor OS ranging from 3 to 6 months following relapse {Jain 2015, Parikh 2015, Sandoval-Sus 2015}.

A second BTK inhibitor, acalabrutinib, was shown to be efficacious in a Phase 1/2 study of 132 subjects with r/r CLL (2 additional subjects had SLL). After a median follow-up of 19.8 months, the ORR was 85% (93% when including partial response [PR] with lymphocytosis), but the CR rate was 2%. The median PFS and OS were not reached {Byrd 2017}. Acalabrutinib has also shown some promise as a treatment for patients with CLL who are intolerant to ibrutinib and have not yet progressed {Awan 2016}. This treatment would not be suitable for patients who have progressed on ibrutinib or developed BTK mutations. Acalabrutinib has been approved for the treatment of adults with CLL as first line therapy as well as in the r/r setting, based on 2 randomized, actively controlled trials (ELEVATE-TN and ASCEND trials) {CALQUENCE 2019}.

Venetoclax is a first-in-class inhibitor of BCL-2 that is approved for patients with r/r CLL who have del17p and at least 1 prior therapy in the US. Venetoclax was also approved by the FDA in May 2019 for first line treatment for adult patients with CLL or SLL {VENCLEXTA 2019}. Approval was based on CLL14 (NCT02242942), a randomized (1:1), multicenter, open label, actively controlled trial of venetoclax in combination with obinutuzumab (VEN +G) versus obinutuzumab in combination with chlorambucil (GClb) in 432 patients with previously untreated CLL with coexisting medical condition. The major efficacy outcome was progression-free survival (PFS) assessed by an independent review committee. The trial demonstrated a statistically significant improvement in PFS for patients who received VEN+G compared with those who received GClb (HR 0.33; 95% CI: 0.22, 0.51; p<0.0001). Median PFS was not reached in either arm after a median follow-up duration of 28 months. The overall response rate was 85% in VEN+G arm compared to 71% in GClb arm, p=0.0007. The trial also demonstrated statistically significant improvements in rates of minimal residual disease negativity (less than one CLL cell per 10^4 leukocytes) in bone marrow and peripheral blood. Overall survival data were not mature at this analysis. In the European Union (EU), venetoclax is approved for use in combination with rituximab for patients with CLL who have received at least 1 prior therapy, and as a monotherapy in those patients with CLL with del17p or TP53mut who are unsuitable for or have not responded to a B-cell receptor pathway inhibitor and those without del17p/TP53mut who have not responded to both chemoimmunotherapy and a B-cell receptor pathway inhibitor. Approvals for venetoclax monotherapy in the r/r setting were based on 2 single-arm Phase 2 trials that demonstrated high ORRs of 60% to 80% but low CR/CRi rates of < 10% {Jones 2018, Stilgenbauer 2016}. A recent study suggests a high rate of Richter's transformation accompanying progression on venetoclax; in an evaluation of 67 subjects across 3 early phase trials, 17 of 25 subjects who progressed manifested Richter's transformation {Anderson 2017}. Even in the era of targeted agents, outcomes for patients with Richter's transformation remain extremely poor with a median OS of 3.3 months in a recent study of 71 subjects following treatments targeting B-cell receptor kinases or BCL-2 {Davids 2017}. Furthermore, venetoclax

has a significant risk of tumor lysis, particularly for patients with a high disease burden, necessitating careful monitoring during intrapatient dose escalation over the course of 5 weeks at the time of initiation of therapy; patients at a high risk and some at an intermediate risk for tumor lysis may require hospitalization during the initial steps of dose escalation for intensive monitoring.

Idelalisib, a first-in-class inhibitor of the p110δ catalytic subunit of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling enzyme, is also approved for use in combination with rituximab for the treatment of patients with relapsed CLL. The results that led to its approval demonstrated a high ORR of 83.6% in subjects previously treated exclusively with chemoimmunotherapy but a limited depth of response (0 CRs) {ZYDELIG 2016}. Idelalisib has not been studied systematically in CLL following treatment with ibrutinib but the results available suggest significantly decreased efficacy, with an estimated ORR to idelalisib of 28% in 1 retrospective study {Mato 2016}. In a larger multicenter study, a retrospective analysis of 683 CLL patients treated with kinase inhibitors (KIs) or venetoclax was conducted {Mato 2017}. Patients treated with ibrutinib (versus idelalisib) as first KI had a significantly better PFS in all settings (frontline, r/r, del17p, complex karyotype). When these patients failed the initial KI and were treated with an alternate KI or venetoclax, they had superior PFS compared with chemoimmunotherapy. In patients who discontinued ibrutinib due to disease progression or toxicity, outcomes were improved if they received venetoclax (ORR of 79%) compared to idelalisib (ORR of 46%).

Allogeneic hematopoietic stem cell transplantation is a potentially curative treatment option for CLL but is used rarely in the era of targeted therapy, as few patients are good candidates due to age and comorbidities. Further, it is accompanied by a significant non-relapse mortality risk from acute and chronic graft-versus-host disease (GVHD) in the first 2 years following transplant for CLL, approaching 30% in some studies, as well as significant morbidity in at least a quarter of patients who do survive {Dreger 2014}. Thus, allogeneic transplant is an unsuitable option for most patients.

CAR-modified autologous T cells offer the possibility of yielding high response rates and long-term durable responses in CLL without the accompanying morbidity and mortality associated with the conditioning treatment or GVHD that accompanies allogeneic transplant. CD19 is a 95 kDa transmembrane protein expressed exclusively in the B-cell lineage from pro-B cells through mature B cells but not on hematopoietic stem cells or plasma cells {Anderson 1984, Gupta 2009, Lin 2004, Nadler 1983, Uckun 1990, Uckun 1988}. CD19 is expressed in a number of B-cell malignancies, including non-Hodgkin lymphoma, CLL, and B-cell acute lymphocytic leukemia {Anderson 1984, Johnson 2009b, Leonard 2001, Nadler 1983, Olejniczak 2006, Rodriguez 1994, Uckun 1988}. Anti-CD19 CAR T cells have demonstrated high rates of durable responses in patients with r/r acute lymphoblastic lymphoma and diffuse large B-cell lymphoma, and clinical trials are currently underway evaluating the benefit in other non-Hodgkin lymphomas. Although the treatment experience to date for CLL has been more limited, the early experience shows high ORRs (55 to 90%) even in patients previously treated with ibrutinib {Kochenderfer 2012, Kochenderfer 2015, Porter 2015, Siddiqi 2019, Siddiqi 2018, Turtle 2017}. Consistent with a marked depth of response in response to anti-CD19 CAR T cells, a subset of patients demonstrate an absence of disease relapse years following a single treatment.

2.2. KTE-X19

Kite Pharma, Inc. (hereafter referred to as the sponsor), is focused on the development and commercialization of engineered autologous cell therapy products that harness the power of a patient's own immune system to selectively target and eradicate cancer cells. Kite is developing an anti-CD19 CAR T-cell product for treatment of patients with r/r B-cell malignancies that express CD19. CD19 is expressed by most B-cell malignancies {Johnson 2009a, Leonard 2001, Olejniczak 2006, Rodriguez 1994, Uckun 1988} as well as all normal B lymphocytes in peripheral blood and spleen, but not by granulocytes, monocytes, platelets, erythrocytes, and T lymphocytes {Uckun 1988}. Briefly, the anti-CD19 CAR comprises the following domains: an extracellular anti-human CD19 single-chain variable region fragment (scFv); the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28, a lymphocyte costimulatory receptor that plays an important role in optimizing T-cell survival and function; and the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor complex {Nicholson 1997}. Following CAR engagement with $CD19^+$ target cells, the CD3ζ domain activates the downstream signaling cascade that leads to T-cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity. Additional details regarding the mechanism of action of KTE-X19 can be found in the Investigator's Brochure (IB).

The manufacture of KTE-X19 begins with collection of the patient's own T cells via leukapheresis. For subjects with high numbers of circulating tumor cells (eg, those with B-lineage acute lymphoblastic leukemia, CLL, or mantle cell lymphoma), the T cells in the harvested leukocytes undergo a T-cell enrichment step (referred to as the XLP process) that removes circulating tumor cells from the leukapheresis material. Additional details regarding the manufacture of KTE-X19 are provided in the Investigator's Brochure.

2.3. Prior Anti-CD19 CAR T-cell Study Designs and Results

Refer to the current KTE-X19 Investigator's Brochure (IB) for the most current anti-CD19 CAR T-cell nonclinical and clinical information.

3. STUDY DESIGN AND RATIONALE

3.1. General Study Design

KTE-C19-108 (ZUMA-8) is a Phase 1, multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with r/r CLL and SLL will be assessed to evaluate the safety of KTE-X19. The study will enroll up to approximately 27 subjects with r/r CLL and SLLwill be assessed to evaluate the safety of KTE-X19. Two dose levels may be evaluated in the study.

Dose Level	Total anti-CD19 CAR T cells/kg
Starting Dose	1 x 10^6
Escalating Dose	2 x 10^6

During the study, approximately 15 to 27 subjects with r/r CLL and SLL will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, in collaboration with at least 1 study investigator, will review all data available, including safety and efficacy data and make recommendations regarding further enrollment based on the incidence of DLTs and overall safety profile and cell expansion of KTE-X19. See Section 9.7.

The trial will be separated into two different stages:

In the first stage, subjects with r/r CLL will be enrolled using a 6+3 study design into cohorts described below:

- **Cohort 1:** Up to 9 subjects will be enrolled at 1 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 2 will be based on incidence of DLT in Cohort 1.

- **Cohort 2**: Up to 9 subjects will be enrolled at 2 x 10^6 anti-CD19 CAR T cells/kg.

In the second stage (Amendment 2), subjects with r/r CLL and SLL will be enrolled into Cohort 3 and 4 as described below:

- **Cohort 3:** Three (3) subjects with r/r CLL and SLL with ≤ 1% malignant cells in peripheral blood or absolute lymphocyte count (ALC) < 5,000 cells/µL will be enrolled and dosed KTE-X19 at a dose of 1 x 10^6 anti-CD19 CAR T cells/kg. This is an exploratory cohort. No additional dose levels will be evaluated.

- **Cohort 4**: Up to approximately 15 subjects with r/r CLL who have been previously treated with at least two prior lines of therapy and are receiving ibrutinib as a single agent, or ibrutinib in combination with anti-CD20 antibodies, BCL-2 inhibitors, and PI3k inhibitors as the last line of therapy. Subjects must have received ibrutinib for at least 6 months prior to

screening. Ibrutinib administration will continue up to 30 hours prior to leukapheresis. In case of treatment interruption with ibrutinib, the principal investigator should reach out to the medical monitor to discuss. A 3+3 study approach will be used to evaluate two doses of KTE-X19.

— Cohort 4A:

- Up to 6 subjects using 3+3 approach will be enrolled and dosed at 1 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 4B will be based on incidence of DLT in Cohort 4A.
- **Upon completion of Cohort 4A SRT, it was determined not to enroll subjects in Cohort 4B.*

— Cohort 4B:

- Up to 6 subjects will be enrolled and dosed at 2 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg (escalating dose)

Once a safe dose is established in Cohort 4, additional subjects will be enrolled and dosed for a total of up to twelve (12) subjects at the safe dose level (including those who were enrolled during the SRT evaluation phase). The maximum number of enrolled and dosed in Cohort 4 will be approximately 15 subjects.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- [redacted]
- Lymphodepleting/conditioning chemotherapy
- Investigational product (IP) treatment
- Post-treatment assessment
- Long-term follow-up. After the end of KTE-C19-108, 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 (LTFU), KT-US-982-5968.

For study requirements, refer to the schedule of assessments (SOA), Table 3 and Table 4, and Section 7 for details.

A study schema is included at the end of the protocol synopsis (Figure 1).

3.2. Study Rationale For Cohort 1 and Cohort 2

While chemoimmunotherapy and targeted therapy represent efficacious treatment options for CLL, very few patients are cured by currently available treatment short of allogeneic stem cell transplant, which is itself limited by treatment-associated morbidity and mortality. Since its approval, ibrutinib has become widely used in both previously untreated patients with CLL as well as those with r/r disease.

Second generation BTK inhibitors, such as acalabrutinib, have demonstrated activity in r/r CLL patients who have not progressed with prior ibrutinib treatment or in patients who have become intolerant to ibrutinib{Awan 2016}. Acalabrutinib has been approved for the treatment of adults with CLL as first line therapy as well as in the r/r setting, based on 2 randomized, actively controlled trials (ELEVATE-TN and ASCEND trials) {CALQUENCE 2019}.

Patients who have progressed or are ineligible to receive a BTK inhibitor due to toxicity may have limited options that can offer deeper responses. While venetoclax is approved for previously treated CLL, it shows limited depth of response in this setting with an accompanying significant risk of tumor lysis syndrome and a high rate of progression with Richter's syndrome. Idelalisib has not been studied systematically following ibrutinib treatment though some retrospective analyses suggest limited efficacy. Furthermore, chronic treatment with these approved targeted agents is necessitated by the absence of deep responses or significant rates of MRD−. As treatment with these agents has become more prevalent, the limitations of their accompanying toxicity have also become more evident; treatment discontinuations due to AEs occur in a significant subset of patients {Maddocks 2015, Mato 2018}.

Engineered autologous cell therapy has the potential to yield long lasting durable responses following a single administration. Autologous CAR T cells targeted to CD19 have transformed the treatment landscape for r/r diffuse large B-cell lymphoma and acute lymphocytic leukemia and are under evaluation for a number of additional B-cell malignancies. Early results with anti-CD19 CAR T cells from the National Cancer Institute, University of Pennsylvania, and the Fred Hutchinson Cancer Research Center have demonstrated efficacy in CLL with a tolerable safety profile.

This study will evaluate the safety and tolerability of KTE-X19 in subjects with r/r CLL and SLL who have failed or have become intolerant to a BTK inhibitor.

3.2.1. Rationale for Cohort 3

In this cohort, the sponsor will explore if enrollment of subjects with a diagnosis of r/r SLL or r/r CLL who present with ≤ 1% circulating tumor cells (low tumor burden) in peripheral blood demonstrate meaningful CAR T-cell expansion. One subject enrolled in ZUMA-8 Cohort 1 who presented with a low circulating tumor burden achieved meaningful expansion of CAR T cells and a PR (Data on File). The published experience from the NCI of 8 subjects with r/r CLL treated with anti-CD19 CAR-transduced T cells (using the same construct used in this study) demonstrated a robust expansion of CAR T cells in subjects who had low circulating CLL burden with a median pre-apheresis ALC of 0.54 x 10^3 cells/uL.

A phase 1 study conducted at Memorial Sloan Kettering Cancer Center, investigated CD-19-targeted CAR T-cells incorporating a CD28 costimulatory domain {Geyer 2019}. The study included 16 patients with r/r CLL. The analysis of disease burden (absolute lymphocyte counts) of these patients at the time of CAR T-cell infusion, showed a median value of 2.35 x 10^3 cells/uL, which is lower compared with the median value of 7.2 x 10^3 cells/uL found in 10 subjects dosed with KTE-X19 in ZUMA-8 study, cohorts 1 and 2.

3.2.2. Rationale for Cohort 4 {Geyer 2019}

3.2.2.1. Introduction

Only 10 to 30% of CLL patients treated with chemoimmunotherapy or targeted therapies achieve CR or MRD^-, and 50% of these patients relapse within 3 to 4 years {Bottcher 2012, Strati 2014}. Patients who progress on targeted agents have limited options and shortened OS {Anderson 2017, Mato 2016}.

Initial clinical trials with CAR T cells in r/r CLL aimed to address the feasibility and proof of concept of monotherapy with CAR T cells targeting the pan-B-cell marker CD19. Early clinical results showed ORR of 71% in this heavily pretreated patient population {Turtle 2017}. The immune dysregulation observed in patients with CLL is well characterized, and intrinsic T-cell defects impose a significant barrier to both the feasibility of generating CAR T cells and the responsiveness of the disease to CAR T-cell-based therapy. One of the most critical determining factors for the success of CAR T cells is the expansion and persistence of antigen-specific T cells {Robbins 2004}. Additionally, the response of CLL to CAR T-cell therapy is influenced by the composition of the cellular product and/or T-cell fitness {Fraietta 2018}.

The following preclinical and clinical data are intended to support the rationale of including Cohort 4 in this study, in which subjects must have been exposed to ibrutinib for at least 6 months prior to screening, to test if this exposure prior to leukapheresis has a positive impact on T-cell fitness, with the goal of increasing expansion of CAR T cells through ibrutinib's modulatory effect on T-cell function.

3.2.2.2. Preclinical Data

Ibrutinib exerts its immunomodulatory effects by inhibiting BTK and IL-2 inducible T cell kinase (ITK) signaling. Peripheral blood mononuclear cells (PBMC) from 19 subjects with CLL treated with ibrutinib were evaluated for T-cell phenotype, immune function, and CLL cell immunosuppressive capacity. Results showed that ibrutinib treatment increased in vivo persistence of activated T cells, decreased the Treg/$CD4^+$ T-cell ratio, and diminished the immune-suppressive properties of CLL cells through BTK-dependent and independent mechanisms {Long 2017}. It was demonstrated that the influence of ibrutinib in subjects with CLL also has a direct positive influence on the immunosuppressive capacity of the primary tumor cells, reducing the expression of the immunosuppressive molecules CD200 and BTLA as well as IL-10 production by CLL cells {Long 2017}.

In addition, ibrutinib, through ITK inhibition, enables pleotropic effects on the various T-cell subsets including enhancing expansion of activated T cells, while having no deleterious effects on the central memory T cells (Tcm) or naïve T cells; no collateral expansion of the regulatory T cells (Treg cells); and partially reversing the exhausted T-cell phenotype by reducing the expression of PD-1 and CTLA4 {Long 2017}. Preclinical evidence demonstrated that ibrutinib, when administered concurrently with CAR T cells, improves CAR T-cell engraftment, tumor clearance, and survival in human xenograft models of acute lymphocytic leukemia and CLL {Fraietta 2016}. Specifically, treatment with ibrutinib for ≥ 5 cycles (28 days of treatment was considered 1 cycle) had a positive impact on the impaired T-cell function in patients with CLL through its modulation of T-cell function. In summary, ibrutinib improved expansion of CD19-directed CAR T cells (CTL019) in association with decreased expression of PD-1 on T cells {Fraietta 2016}.

3.2.2.3. Clinical Data

Evidence showed that T cells collected from subjects exposed to ibrutinib had greater ex vivo expansion and a greater fraction of T cells with a Tcm phenotype compared to T cells from subjects with CLL who were not receiving ibrutinib. The ORR for subjects who had received concurrent ibrutinib was 80%, whereas the ORR for all subjects was only 38% {Geyer 2019}.

In a prospective trial combining a humanized CD19-targeted CAR T cell (CTL119) with ibrutinib, the ORR at 3 months in 14 evaluable subjects was 71% with 6 CRs (43%) {Gill 2018}. At 3 months, 17 of 18 subjects (94%) demonstrated a morphologic CR within the marrow and 15 of 17 subjects were MRD^- by high resolution flow cytometry. Fourteen of 18 subjects were MRD− by IgH sequencing.

In a Phase 1/2 study, it was observed that subjects who received concurrent treatment with ibrutinib (420 mg/day) from at least 2 weeks before leukapheresis until at least 3 months after JCAR014 CAR T-cell infusion had a higher proportion of responders (CR and PR) by International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria in the ibrutinib cohort (14 of 16 evaluable subjects, 88%) compared to the non-ibrutinib cohort (10 of 18 evaluable subjects, 56%) {Gauthier 2018}.

In a Phase 1 clinical trial investigating CD19-targeted CAR T cells incorporating a CD28 costimulatory domain (19-28z), ex vivo expansion of T cells and proportions of $CD4^+/CD8^+$ CAR T cells with a $CD62L^+$ $CD127^+$ immunophenotype were significantly greater in subjects who were receiving ongoing therapy with ibrutinib at leukapheresis {Geyer 2019}. Three of 12 evaluable subjects with CLL receiving conditioning chemotherapy with cyclophosphamide/bendamustine or fludarabine/cyclophosphamide achieved CR (2 had MRD− CR). All subjects achieving CR remained progression-free with a median follow-up of 53 months.

A recent pilot study reported the treatment of 19 subjects with CLL with anti-CD19 CAR T-(4-1BB and $CD3_z$ signaling domains) These patients were treated after ibrutinib failure. {Gauthier 2020}. Patients were heavily pretreated (median number of prior therapies was 5), and 17 subjects (89%) had high-risk cytogenetics (del17p and/or complex karyotype). The minimal time to exposure to ibrutinib was 2 weeks prior to leukapheresis and ibrutinib was

continued for at least 3 months after CAR T-cell infusion. Thirteen subjects (68%) received ibrutinib as planned in the protocol without dose reduction. The ORR by IWCLL criteria assessed at 4 weeks after the infusion was 83%, and 61% achieved MRD^-. The 1-year OS and PFS probabilities were 86% and 59%, respectively. Compared to subjects with CLL who were treated with CAR T cells without ibrutinib, Subjects treated with CAR T cells with concurrent ibrutinib, compared to subjects treated with CAR T cells without ibrutinib, showed was lower severity of cytokine release syndrome (CRS) and lower serum concentrations of CRS-associated cytokines despite equivalent in vivo CAR T-cell expansion.

Other non-randomized studies to prospectively evaluate the combination of ibrutinib and CAR T cells are currently ongoing (NCT03331198, NCT02640209).

In summary, in order to improve the acquired T-cell dysfunction in r/r CLL, prior exposure to ibrutinib, before leukapheresis may lead to improved T-cell fitness and thereby enhance the ability of CAR T cells to expand in vivo and exert antitumor effects.

3.2.3. Rationale for Conditioning Chemotherapy

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in preclinical models, which demonstrate that the depth and duration of lymphodepletion correlates with anti-tumor activity of the adoptively transferred tumor-specific CD8+ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen-presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine combination is a potent lymphodepleting regimen. Cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) are both given for 3 consecutive days. This combination has been studied in subjects with B-cell malignancies and was tolerated by this population {O'Brien 2001} and was also used in the ZUMA-1 trial {Neelapu 2017}.

3.2.4. Rationale for KTE-X19 Dose

The initial dose level of 1 x 10^6 anti-CD19 CAR T cells/kg has been previously shown to be safe and tolerable for subjects with r/r acute lymphocytic leukemia (KTE-C19-103/ZUMA-3) and mantle cell lymphoma (KTE-C19-102/ZUMA-2). The 2 dose levels of KTE--X19 proposed for this study have been previously evaluated in the KTE-C19-103 study, with only 1 DLT at the 2 x 10^6 anti-CD19 CAR T cells/kg dose level; this dose level has also been deemed to be safe and tolerable for subjects with mantle cell lymphoma in KTE-C19-102. KTE-X19 is CCI [redacted] approved by the FDA at a dose of 2 x 10^6 anti-CD19 CAR T cells/kg for the treatment of patients with r/r large B cell lymphoma.

3.3. Overall Risk and Benefit Assessment

Kite is developing KTE-X19, an anti-CD19 CAR T-cell product for treatment of patients with r/r B-cell malignancies that express CD19.

While chemoimmunotherapy and targeted therapy represent efficacious treatment options for CLL, the limited depth of response from currently approved targeted agents for CLL underlies the ongoing inability to yield durable responses with finite therapy or to result in a cure for patients with CLL. Also, while allogeneic hematopoietic stem cell transplantation is a potentially curative treatment option for CLL, it is now rarely used as few patients are appropriate candidates due to age and comorbidities.

CAR T-cell therapy offers the possibility of yielding deep MRD− responses and long-term durable responses in CLL without the morbidity and mortality associated with the conditioning treatment or the GVHD of allogeneic transplant. Although the treatment experience to date for CLL has been limited, the early experience shows high rates of response (55 to 90%), with up to 88% MRD^-, even in subjects previously treated with ibrutinib {Kochenderfer 2012, Kochenderfer 2015, Porter 2015, Siddiqi 2019, Siddiqi 2018, Turtle 2017}. A subset of subjects remain relapse-free years following a single treatment, evincing a marked depth of response due to anti-CD19 CAR T cells.

KTE-X19 is administered as a single dose following conditioning chemotherapy, and the majority of AEs occur within 30 days of infusion. AEs, which can be severe or even fatal, are well defined, generally reversible, and manageable with no apparent long-term consequences other than B-cell aplasia. The most common events were cytopenias, which are expected from the conditioning chemotherapy, as well as infections, CRS, and neurologic events. Guidelines for management of these AEs are described in the Investigator's Brochure (IB), Section 6.5.

The IB also contains the current understanding of the pathophysiology of CRS/neurotoxicity, and clinical trials experience across KTE-X19 studies to provide context and rationale for management. Furthermore, all sites are trained by the Kite medical monitor on toxicity management including CRS and neurological toxicity at the site initiation visit, and new sites are retrained at first dosing of KTE-X19. Kite provides regular Investigator calls and meetings as well as a toxicity management tool so that sites have quick access to relevant information.

In summary, the rates and durations of high quality clinical responses anticipated within the KTE-X19 study design, the demonstrated safety profile of KTE-X19 to date in other malignant B-cell diseases, and the planned safety monitoring plan (SRT) in this study suggest that the benefits of study participation will outweigh the risks for these subjects with r/r CLL and SLL.

3.4. Participating Sites

Approximately 22 centers located in North America and Europe will participate in this study. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

3.5. Number of Subjects

Participants in this trial will be referred to as "subjects." It is anticipated that up to approximately 27 subjects will be enrolled and dosed in this study.

3.6. Replacement of Subjects

Subjects may continue to be enrolled until the specified approximate number of subjects are dosed with KTE-X19 in Phase 1 for safety evaluation (see Section 10.6).

3.7. Study Duration

3.7.1. Study Duration for Individual Subjects

The duration of the study 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 LTFU study, KT-US-982-5968 (discussed in Section 3.7.3).

3.7.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes at least 3 months of assessments (the post-treatment follow-up period), is considered lost to follow-up, withdraws consent, or dies. Upon activation of KT-US-982-5968 at subject study site, the subject will be offered the opportunity to complete long-term follow-up assessments under the KT-US-982-5968 protocol.

3.7.3. Long-term Follow-up

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, 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 7.13).

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

4. SUBJECT IDENTIFICATION ASSIGNMENT

Each subject who enters the screening period, which starts when the subject signs the informed consent form, will receive a unique subject identification (ID) number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. The subject identification number will never be changed even if the subject is rescreened.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrollment:

101. Documentation of relapsed or refractory CLL and SLL; subjects must have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor

    a. Cohort 1 and 2: Subjects with r/r CLL who have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor

    b. Cohort 3: Subjects with r/r CLL and SLL must present with ≤ 1% circulating tumor cells in peripheral blood or ALC < 5000 cells/µL. Subjects must have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor.

    c. Cohort 4: Subjects with r/r CLL who have received at least 2 prior lines of treatment and must have received ibrutinib as a single agent or in combination with anti-CD20 antibodies, BCL-2 inhibitors, and PI3k inhibitors for at least 6 months as the last line of therapy prior to screening. Ibrutinib administration will continue up to 30 hours prior to leukapheresis. In case of treatment interruption with ibrutinib, the principal investigator should reach out to the medical monitor to discuss.

102. An indication for treatment per IWCLL 2018 criteria {Hallek 2018} and radiographically measurable disease (at least 1 lesion > 1.5 cm in diameter)

103. Adequate hematologic function as indicated by:

    a. Platelet count ≥ 50×10^9/L

    b. Neutrophil count ≥ 0.5×10^9/L

    c. Hemoglobin ≥ 8 g/dL

    Unless lower values are attributable to CLL

104. Adequate renal, hepatic, cardiac and pulmonary function defined as:

    a. Creatinine clearance (as estimated by Cockroft-Gault) ≥ 60 mL/min

    b. Serum ALT/AST ≤ 2.5 x upper limit of normal (ULN)

    c. Total bilirubin ≤ 1.5 mg/dL unless subject has Gilbert's syndrome

    d. Left ventricular ejection fraction (LVEF) ≥ 50%, no evidence of pericardial effusion, no NYHA class III or IV functional classification, no clinically significant arrhythmias

e. No clinically significant pleural effusion

f. Baseline oxygen saturation > 92% on room air

105. Age 18 or older

106. ECOG performance status of 0 or 1

107. Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

108. At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy or BTKi (ibrutinib or acalabrutinib) at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists)

5.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for enrollment:

201. A history of treatment including any of the following:

a. Prior CD19 directed therapy

b. Treatment with alemtuzumab within 6 months before enrollment

c. Allogeneic hematopoietic stem cell transplant (SCT) or donor lymphocyte infusion (DLI) within 6 months prior to enrollment

d. Live vaccine administration within 4 weeks before enrollment

e. Systemic immunosuppression or systemic treatment for any autoimmune disease not related to CLL in the 2 years before enrollment

202. Acute GVHD grade II-IV by Glucksberg criteria or severity B-D by IBMTR index

203. History of autoimmune disease resulting in end-organ injury unless attributable to CLL (eg, ITP, AIHA)

204. Diagnosis of Richter's transformation or a history of malignancy. Exceptions include:

a. Non-melanoma skin cancer or carcinoma in situ (eg, skin, cervix, bladder, breast)

b. Superficial bladder cancer

c. Asymptomatic localized low grade prostate cancer for which watch-and-wait approach is standard of care

d. Any other cancer that has been in remission for > 3 years prior to enrollment

205. History of severe hypersensitivity reaction attributed to aminoglycosides or any of the agents required for treatment in this study

206. CNS disease including:

a. Known presence of involvement by CLL/SLL

b. History of any CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome (PRES), or cerebral edema with confirmed structural defects (eg, by whole-neuroaxis magnetic resonance imaging [MRI])

Note: Subjects with a history of seizures requiring antiseizure therapy are excluded.

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

208. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months before enrollment

209. History of symptomatic deep vein thrombosis or pulmonary embolism requiring systemic anticoagulation within 6 months before enrollment. Subjects taking prophylactic anticoagulation are eligible.

210. Primary immunodeficiency

211. History of human immunodeficiency virus (HIV) infection or acute or chronic active hepatitis B or C infection. Subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Disease Society of America (IDSA) guidelines or applicable country guidelines.

212. Presence of active fungal, bacterial, viral infection or any infection requiring antimicrobial treatment for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite medical monitor

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

214. Women of childbearing 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.

215. Subjects of childbearing potential who are not willing to practice birth control from the time of consent through 6 months after the administration of conditioning chemotherapy or KTE-X19, whichever is longer.

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

217. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

6. PROTOCOL TREATMENT

6.1. Study Treatment

6.1.1. Leukapheresis

Leukapheresis refers to the procedure for collecting PBMCs that are used to manufacture the subject-specific KTE-X19.

Subjects will undergo leukapheresis to obtain T cells for the manufacturing of KTE-X19. Leukapheresed cells obtained at participating centers will be shipped to the sponsor's manufacturing facility as described in the Investigational Product Manual (IPM).

CCI [redacted]

6.1.3. Conditioning Chemotherapy

Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of KTE-X19.

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.

6.1.3.1. Fludarabine

Fludarabine phosphate (hereafter, fludarabine) 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.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.1.3.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative that acts as an alkylating agent following conversion to active metabolites in the liver and has potent immunosuppressive activity. The serum half-life after intravenous (IV) administration ranges from 3 to 12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

6.1.3.3. 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 should be administered per institutional guidelines. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.1.4. KTE-X19

KTE-X19 is the IP for this study.

KTE-X19 is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy and cream to yellow color. The cryostorage bag containing KTE-X19 arrives frozen in a liquid nitrogen dry shipper. The bag must be stored in vapor phase of liquid nitrogen and remain frozen until the subject is ready for treatment to assure that 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. The product is labelled per local regulations with the subject's unique subject ID number assigned at the time of screening. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, 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 administration start/stop time, will all be noted in the subject medical record.

The product must not be thawed until the subject is ready for the infusion. Refer to the IPM for details and instruction on storage, thawing, and administration of KTE-X19.

There have been no instances of accidental overdose of subjects in this program to date. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of KTE-X19 or any products that support the management of KTE-X19 (eg, cryostorage bags, subject ID labels) are identified, research staff should report the problem per the instructions in the IPM.

6.2. Concomitant Therapy

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

Investigators may prescribe any concomitant therapies deemed necessary to provide adequate supportive care except those medications listed in Section 6.3.

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

Table 1. Reporting Requirements for Concomitant Medications

Subjects who screen-fail	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.	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 anticancer 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. • 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.

Specific concomitant therapy collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.3. Excluded Medications

Excluded medications refer to treatment that is not to be administered, unless otherwise specified, during the conduct of the study.

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 administration.

Systemic corticosteroids may not be administered as premedication to subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). Such subjects should undergo non-contrast CT scans instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after KTE-X19 administration unless used to manage severe KTE-X19-related toxicities. Other medications that might interfere with the evaluation of KTE-X19, such as nonsteroidal anti-inflammatory agents, should also be avoided for the same 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.

Non-study treatment for CLL/SLL is prohibited prior to disease progression on study.

If permissibility of a specific medication/treatment is in question, contact the Kite medical monitor.

6.4. Subsequent Therapy

Subsequent therapy refers to treatment administered after KTE-X19 that is necessary to treat a CLL/SLL.

Subsequent therapy such as non-study specified chemotherapy, immunotherapy, targeted agents, SCT, or radiation therapy, will be recorded for all enrolled subjects until one of the following happens: the subject transitions to the KT-US-982-5968 LTFU study, is considered lost to follow-up, withdraws consent, or dies.

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

7. STUDY PROCEDURES

Research staff should refer to the SOA Table 3 and Table 4 for an outline of the procedures required. Additional information related to a few study assessments/procedures is further described below.

The visit schedule is calculated from KTE-X19 infusion on Day 0.

Refer to the CRF completion guidelines for data collection requirements and best practices for documentation of study procedures.

7.1. Informed Consent

Before a subject participates in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequately explaining the study design, anticipated benefits, and potential risks. Subjects should sign the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent form (ICF) before any study-specific activity or procedure is performed.

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

7.2. Screening

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected in 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.

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

After written informed consent has been obtained, Kite Pharma, Inc., will assign a screening number to the subject, as described in Section 7.1.

See Section 7.2.1 for the study procedures for subjects who rescreen into the study.

Only subjects who meet the eligibility criteria listed in Section 5 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.

Refer to the SOA for a listing of study procedures to be completed during the screening period.

7.2.1. Rescreening

Subjects who do not meet the eligibility criteria during the 28-day screening period will be permitted to rescreen one time. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, it is only necessary to perform the procedure(s)/assessment(s) that did not originally meet the eligibility criteria; all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs, or leukapheresis is delayed more than 28 days from the signing of the original informed consent, subjects must be re-consented and repeat all screening procedures/assessments.

7.3. Demographic Data

Demographic data will be collected as 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 a possible association between these variables and subject safety and treatment effectiveness.

7.4. Medical and Treatment History

Relevant medical history prior to the start of AE reporting (see Section 9.2) will be collected. Relevant medical history is defined as data on the subject's current medical condition that would be typically shared in a referral letter. 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. All findings will be recorded in the CRFs.

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.

7.5. Physical Exam, Vital Signs, and Performance Status

Physical exams will be performed during screening and at times noted in the SOA. All physical exam changes noted in subsequent exams when compared to the baseline exam will be reported as AEs per Section 9.1. Subjects with new-onset symptoms related to CRS should undergo physical exam at least daily until symptoms resolve to baseline.

Vital signs, including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature, will be monitored and recorded at screening and at times outlined in the SOA. In addition to the time points outlined in the SOA, it is recommended that vital signs are monitored during and after the KTE-X19 infusion and 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.

7.6. Cardiac Function

Each subject's cardiac function, as measured by LVEF, will be assessed during the screening period to confirm study eligibility. No evidence of pericardial effusion will also be confirmed, per study eligibility criteria. LVEF may be assessed by echocardiogram (ECHO) or MUGA, and pericardial effusion may be assessed by ECHO or CT/MRI. Imaging that was performed after the subject's last chemotherapy treatment may also be used to confirm eligibility, provided that it occurred ≤ 28 days prior to signing the consent.

To establish a baseline, a 12-lead electrocardiogram (ECG) will also be performed during the screening period.

7.7. Neurological Examination

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. Changes in neurological status (level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, and neuropsychological findings (eg, speech, cognition and emotion)) should be reported as an AE per Section 9.

For new onset of neurologic symptoms (eg, severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam), neurologic assessment should be performed at least daily until symptoms resolve to baseline. In addition, brain imaging should be considered.

Subjects with new onset Grade ≥ 2 neurologic symptoms post-KTE-X19 infusion will have a lumbar puncture (LP) performed to evaluate for potential causes. A portion of the cerebrospinal fluid (CSF) will be submitted to the central lab for evaluation of KTE-X19 levels and cytokines.

7.8. Disease Assessment

Binet and Rai staging will be assessed at screening (Appendix 1). Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease response assessments will be per IWCLL 2018 criteria {Hallek 2018}, (Appendix 3). Laboratory samples to assess disease response will be collected and evaluated per the SOA and are outlined in Section 7.14.

7.8.1. Radiology Assessment

Diagnostic quality contrast-enhanced (unless contraindicated) CT (preferred) or MRI of the head, neck, chest, abdomen and pelvis must be performed within 28 days before enrollment to confirm eligibility. Scans obtained as part of SOC before signing of the ICF and within 56 days before enrollment can be used for eligibility.

If the subject received treatment for CLL/ SLL after the eligibility images were obtained, then additional baseline images must be taken after the completion of CLL/SLL treatment and within 28 days before conditioning chemotherapy. CCI [redacted]

The same imaging modality should be used when possible for post-treatment response assessments as outlined in the SOA and in the event of suspected disease progression. See Section 7.7 for imaging requirements for neurological symptoms.

7.8.2. Bone Marrow Assessment

A bone marrow aspirate and biopsy is required per the SOA at the following timepoints:

- Screening or prior to conditioning chemotherapy (if applicable)

  CCI [redacted]

- Day 28
- Month 6
  - The Month 6 bone marrow evaluation is not required if the subject is confirmed to be MRD- per bone marrow evaluation prior to Month 6.
- Subsequent to any evaluation following Day 28 when the subject's hematologic and radiographic response becomes consistent with CR/CRi with peripheral blood MRD- in order to establish a CR/CRi with bone marrow MRD- per IWCLL 2008 criteria (see Appendix 3).

In addition, a bone marrow evaluation (biopsy and/or aspirate) should be performed at the following timepoints:

- For persistent cytopenias and to diagnose hemophagocytic lymphohistiocytosis (HLH) if appropriate. Refer to the IB for additional information.
- At the time of progressive disease.

CCI [redacted]

[redacted]

Whenever obtained, a portion of the bone marrow aspirate and biopsy specimen must be sent to the central laboratory for analysis.

7.9. Cell Collection and Study Treatment Schedule and Administration

7.9.1. Leukapheresis

7.9.1.1. Requirements for Initiating Leukapheresis

Before leukapheresis commences, the following criteria must be met:

- Subjects must remain eligible per the eligibility criteria outlined in Section 5 prior to the start of leukapheresis.
- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and results are outside the eligibility criteria listed in Section 5, contact Kite's medical monitor prior to proceeding with leukapheresis.
- No evidence or suspicion of an infection
- 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
- If criteria are not met, leukapheresis must be delayed until the event resolves. If leukapheresis is delayed more than 5 days after eligibility confirmation, baseline complete blood count (CBC) with differential and chemistry panel must be repeated. If results are outside the eligibility criteria listed in Section 5, contact the medical monitor prior to proceeding with leukapheresis.

The leukapheresis visit should occur within approximately 5 days of eligibility confirmation. After a subject commences leukapheresis, the subject will be considered enrolled into the study.

After the above criteria are met, mononuclear cells will be obtained by leukapheresis (12 to 15 L) apheresis with a goal to target approximately 5 to 10 x 10^9 mononuclear cells. The leukapheresed cells are then packaged for expedited shipment to the manufacturing facility as described in the IPM.

Refer to the SOA Table 3 for a listing of study procedures to be completed on the leukapheresis collection day.

CCI [redacted]

[redacted]

7.9.3. Conditioning Chemotherapy and KTE-X19 Infusion

Administration of CAR T 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 (eg, "tumor fever," elevated C-reactive protein [CRP]) are diagnoses of exclusion that require a documented workup to establish. Conditioning chemotherapy and KTE-X19 infusion should be initiated only once it is reasonably assured that cell infusion can safely proceed.

Refer to Section 7.9.4 for Requirements to Work-up Potential Infectious and/or Inflammatory States.

7.9.3.1. Conditioning Chemotherapy Period

7.9.3.1.1. 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 7.9.4 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38 degrees Celsius within 72 hours of conditioning chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- White blood cell (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 segs/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 head, ears, eyes, nose, and throat (HEENT), cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of antimicrobials 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.

7.9.3.1.2. Conditioning Chemotherapy Administration (Day –5 Through Day –3 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 –5. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day –5 and through Day –3, with 2 rest days (Day –2 and Day –1) before receiving KTE-X19. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

Before conditioning chemotherapy commences, the criteria outlined in Section 7.9.3.1.1 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.

- IV hydration with a balanced crystalloid according to institutional guidelines prior to administration of cyclophosphamide on the day of infusion

- Cyclophosphamide 500mg/m^2/day IV over approximately 30-60 minutes

- Fludarabine 30mg/m^2/day IV over approximately 30 minutes

- Additional IV hydration with a balanced crystalloid according to institutional guidelines to be administered upon completion of the cyclophosphamide infusion

- Mesna to be administered per institutional guidelines

Subjects should be instructed to drink plenty of liquids during chemotherapy and throughout the 24-hour period following chemotherapy (approximately 2 L/24 hours). In general, subjects should be kept well-hydrated but closely monitored to prevent fluid overload.

Refer to the SOA Table 3 for a listing of study procedures to be completed during the KTE-X19 conditioning chemotherapy period.

7.9.3.2. KTE-X19 Treatment Period

7.9.3.2.1. Requirements for Initiating KTE-X19 Infusion

If any of the following criteria are met prior to the initiation of KTE-X19 infusion, then the work-up listed in Section 7.9.4 must be performed to determine the potential cause if there is no identified source of infection.

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

Additionally:

- 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, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before KTE-X19 (prophylactic use of antimicrobials 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.

7.9.3.2.2. Hospitalization for KTE-X19 Infusion

Subjects will be hospitalized to receive KTE-X19 infusion and will remain in the hospital for at least 7 days to monitor for signs and symptoms of CRS and neurologic events. Post infusion monitoring of patients must be for a minimum of 7 days unless otherwise required by country regulatory agencies. Refer to Appendix 4.

Subjects should not be discharged from the hospital until all KTE-X19-related non-hematological toxicities resolve to ≤ Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (eg, renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain in a hospital for ongoing KTE-X19-related fever, hypotension, hypoxia, or ongoing neurologic events > Grade 1, or if deemed necessary by the investigator.

Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following KTE-X19 infusion. Subjects should be advised to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks following KTE-X19 infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

7.9.3.2.3. 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 medical monitor.

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

7.9.3.2.4. KTE-X19 Administration Day 0

KTE-X19 will be administered at one of the dose levels as outlined in Section 3.1.

Refer to the SOA for a listing of study procedures to be completed during the KTE-X19 treatment period.

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. Vital signs should be measured during and after KTE-X19 treatment (See Section 7.5). The IPM must be reviewed prior to administration of KTE-X19.

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

7.9.4. Requirements to Work-up Potential Infectious and/or Inflammatory States

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 antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x2 bottles each, cultured for 48 hours) and urinalysis 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 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)
- If a CNS process is suspected, appropriate brain imaging and subsequent LP 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 > 100mg/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.

7.10. Toxicity Management

To date, the following important risks have been identified with KTE-X19: CRS, neurologic toxicities, infections, hypogammaglobulinemia, and cytopenias. Refer to the current KTE-X19 IB for details regarding these events and management guidance for potential risks associated with KTE-X19. Refer to the SOA (Table 3 and Table 4) for the timing of evaluations for CRS and neurological related symptoms.

As the safety experience with KTE-X19 increases, the management guidance may be updated. Therefore, it is important to 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 possible complications associated with malignancy and cancer treatment.

7.11. Laboratory

7.11.1. Local Lab Analysis

Assessments listed in Table 2 will be performed at the local laboratory at the time points indicated in the SOA.

Table 2. Clinical Laboratory Parameters

Serum Chemistries	Hematology	Other
Albumin	CBC with differential[b]	CRP
ALT/GPT		Ferritin
ALP		Pregnancy test
AST/GOP		Viral testing[c]
Bicarbonate total		
Bilirubin total[a]		
BUN or urea[a]		
Calcium total		
Chloride		
Creatinine		
Glucose		
LDH		
Magnesium total		
Phosphorus		
Potassium		
Sodium		
Uric acid[b]		

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; GOP, serum glutamic-oxaloacetic transaminase; GPT, serum glutamic-pyruvic transaminase; LDH, lactate dehydrogenase.

a If BUN test cannot be analyzed by the local lab, urea should be analyzed. If total bilirubin is elevated, then direct bilirubin should be obtained.
b Per institutional guidelines but must include WBC, neutrophils or ANC, lymphocytes or ALC, hemoglobin, platelets.
c In European Union (EU) sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations, unless otherwise required by country regulatory agencies (refer to Appendix 4 for details), to evaluate for active infection (see SOA)

7.11.2. Central Laboratory Analyses

The following biospecimens will be sent to the central laboratory(ies) for sample processing, accessioning, and distribution to specialty laboratories or Kite:

- Bone marrow biopsy and aspirate, nodal biopsy and/or peripheral blood sample for CLL/SLL immunophenotyping, confirmation of diagnosis and genetic analyses related to CLL/SLL prognostic factors
- Peripheral blood for PK (levels of anti-CD19 CAR T cells), replication-competent retrovirus (RCR) testing, and assessment of B-cell aplasia and immune reconstitution
- Serum for pharmacodynamics (cytokine levels) and immunogenicity testing (development of antibodies against KTE-X19)
- CSF or other bodily fluids to monitor for the presence of anti-CD19 CAR T cells, other immune cell subsets and for the purpose of understanding the mechanism of action and safety profile of KTE-X19

Samples are obtained at the times indicated in the SOA. Complete instructions regarding sample processing and submission to central laboratory(ies) are provided in the Central Laboratory Manual.

CCI [redacted] Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who, in turn, can contact the sponsor. The investigator should provide the sponsor with the study and subject number so that the sample can be located and destroyed. 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 from these samples will be entered in the study database.

Multiple specialty laboratories may be employed for specific analyses, such as baseline/archival tumor assessments, confirmation of diagnosis, PK, pharmacodynamics, and special safety analyses (immunogenicity and RCR testing). Refer to the Central Laboratory Manual for instructions regarding submitting such samples to the appropriate laboratory.

Central lab immunophenotyping of peripheral blood obtained at screening will confirm the diagnosis of CLL/SLL.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

7.11.2.3. Product Characteristics

Samples of apheresis material or final product will be retained and tested by the sponsor or specialty laboratory for the purpose of understanding the mechanism of action and safety profile of KTE-X19.

7.11.2.4. Immunogenicity

Immunogenicity will be evaluated utilizing a screening enzyme-linked immunosorbent assay (ELISA) designed to detect antibodies present in serum that react against the murine monoclonal antibody FMC63, the parent antibody from which the scFv utilized in the KTE-X19 product is derived.

Blood draws for determination of the presence of anti-FMC63 antibodies using the screening assay will be performed at intervals outlined in the SOA or as clinically indicated.

In the event of a positive result, a qualified confirmatory assay will be utilized to validate positive results observed in the screening assay. Analysis of PK profiles and clinical outcomes in

subjects with a positive screening or confirmatory result at baseline or after treatment with KTE-X19 will also be conducted to determine the impact of anti-FMC63 antibodies on the efficacy and safety of KTE-X19 therapy.

Immunogenicity will also be addressed by a manual review of AE terms indicative of infusion-related events and anaphylactic reactions among subjects who test positive for these antibodies.

7.11.2.5. RCR Testing

KTE-X19 comprises T cells transduced with a γ-retroviral vector; hence, there is a theoretical risk for RCR developing in exposed subjects. Additional information is provided in the IB.

RCR 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 to 15 years or as clinically indicated. Samples for RCR testing are collected as part of the blood draw for PBMCs as noted in the SOA.

7.12. Post-treatment Assessment Period

After completing KTE-X19 infusion, all subjects will return to the clinic for post-treatment follow-up visits and complete the study procedures and assessments per the SOA.

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 childbearing potential
- Proceed to the long-term follow-up period (see Section 7.14 and the SOA for details).

Following the initial hospitalization for the KTE-X19 infusion, if the subject is hospitalized with any KTE-X19 related AE, 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

7.13. 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, for up to 15 years. Subjects will begin the long-term follow-up period after they complete the post-treatment assessment period. Refer to the SOA for a listing of study procedures and disease assessments to be completed during the long-term follow-up period.

After completion of at least 3 months of assessments in the KTE-C19-108 study (refer to Section 3.7.2), all subjects who received an infusion of KTE-X19 will be given the opportunity to transition to a separate LTFU study, KT-US-982-5968. Upon activation of KT-US-982-5968 at each study site, subjects will be asked to provide informed consent and complete the remaining time of their LTFU period.

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

- Survival status
- Serious adverse event (SAE) reporting (see Section 9)
- Concomitant medications documentation (see Section 6.2)
- Subsequent therapy for CLL/SLL (see Section 6.4)
- Blood draw for:
  - PBMCs
  - If applicable anti-KTE-X19 antibodies (see SOA, Section 7.14).

Subjects who are enrolled, but do not receive KTE-X19 treatment, will be followed only until completion of this study and will undergo the following assessments at the time points outlined in the SOA, unless otherwise noted:

- Disease assessment per SOC
- Survival status
- Subsequent therapy for the treatment of CLL/SLL (see Section 6.4)
- AE/SAE reporting (refer to Section 9)
- Concurrent therapies (see Section 6.2)

Subjects may also be contacted by telephone to confirm survival status and subsequent anticancer therapy use. If the subject fails to return to the clinic for a scheduled protocol-specific visit, sites will need to make 2 attempts, using both the telephone and either mail or email 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, then the subject will be considered lost to follow-up, and no additional contact will be required. However, sites will be required to continue to provide survival status as permitted by local regulations.

7.14. Schedule of Assessments

Table 3. Schedule of Assessments

Procedures	Screening	Leukapheresis (Enrollment)	CCI	Conditioning chemotherapy			KTE-X19 Administration Period [a]		Post-treatment Follow-up All Post-treatment visits are calculated from Day 0			
Day	≤28 days before enrollment	≤ approx. 5 days after eligibility confirmation		D-5	D-4	D-3	KTE-X19 Infusion D0	D1 to 7[r]	Day 14 (± 2 days)	Day 28 (± 3 days)	Week 8 (± 1 week)	Month 3 (± 2 weeks)
Medical history	X											
Physical exam [a]	X			X			X [a]		X [a]	X	X	X
Weight (plus height at screening)	X	X										
Vital signs [b]	X [b]	X [b]							X	X	X	X
ECOG performance status	X											
Neurological assessment [c, k]	X						X [c,k]	QOD[c,k]	X [c,k]			
Disease Assessment	X									X	*X*[h]	X
ECG	X											
ECHO/MUGA/Chest CT/MRI [d]	X [d]											
CT or MRI [e]	X [e]									X		X
Local Labs:												
Pregnancy test (serum or urine)	X	X[r]		X[r]								X
Chemistry panel	X	X					X	X	X	X	X	X
CBC w/differential	X	X					X	X	X	X	X	X
LDH [f]				X			X [f]	X [f]				
CRP/ferritin [f]		X					X [f]	X [f]				
Lumbar puncture/CSF [g]								*X* [g]	*X* [g]			
Serology (EU sites)[l]	X[l]	X[l]										
Central Labs:												
Bone marrow biopsy and aspirate[h]	X									X	*X*[h]	*X*[h]

CCI

Procedures	Screening	Leukapheresis (Enrollment)	CCI	Conditioning chemotherapy			KTE-X19 Administration Period [a]		Post-treatment Follow-up All Post-treatment visits are calculated from Day 0			
Day	≤28 days before enrollment	≤ approx. 5 days after eligibility confirmation		D-5	D-4	D-3	KTE-X19 Infusion D0	D1 to 7[r]	Day 14 (± 2 days)	Day 28 (± 3 days)	Week 8 (± 1 week)	Month 3 (± 2 weeks)
Blood draw for Anti-KTE-X19 antibodies [j]		X										X[j]
Blood draw for PBMCs [k]	X							D7[k]	X[k]	X[k]	X[k]	X
Blood draw for Cytokines [k]				X			X	D1,4,7[k]	X[k]	X[k]		X
Lumbar puncture/CSF[g]								X[g]	X[g]			
Leukapheresis		X[b]										
CCI												
Conditioning chemotherapy (Fludarabine/Cyclophosphamide)				X	X	X						
KTE-X19 infusion/Hospitalization							X	X				
AE/SAE[m] / Con meds[n] / Subsequent therapy for CLL/SLL[o] / Survival status[p]	X	X		X	X	X	X	X	X	X	X	X

Table 4. Long-term Follow-up Assessments

Procedure		Long-term Follow-up Period[s] Each visit calculated from Day 0 (± 28 day window)												
Visit frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72, then annually through Year 15**
Physical exam	X	X	X	X	X	X	X							
Disease Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT or MRI[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bone marrow biopsy and aspirate [h]	X [h]													
CCI														
Local lab:														
CBC w/differential	X	X	X	X	X	X	X	X	X	X	X	X	X	
Central labs:														
Blood draw for PBMC [k]	X	X	X		X		X		X		X		X	X
Blood draw for Anti-KTE-X19 antibodies [j]		*X* [j]												
Targeted / AE/SAEs [m]	X	X	X	X	X	X	X	KTE-X19-related SAEs [n]						
Targeted Con Meds [n]	X	X	X	X	X	X	X							
Subsequent therapy for CLL/SLL[o] / Survival status[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes for Table 3 and Table 4

a **Physical exam (Section 7.5)**: Subjects with new-onset symptoms related to CRS should undergo physical exam at least daily until symptoms resolve to baseline.

b **Vital signs (Section 7.5):** Includes blood pressure, heart rate, respiration rate, oxygen saturation, and temperature. Height will be collected at screening. Vitals will be monitored during and after the KTE-X19 infusion and as clinically indicated. Weight should be taken on the day of leukapheresis.

c **Neurologic assessment (Section 7.7):** A neurological assessment will be performed at screening, on Day 0 prior to KTE-X19 infusion, on Day 1 and every other day during the KTE-X19 hospitalization/observation period, which must last a minimum of 7 days.
- For new onset of neurologic symptoms (eg, severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam), neurologic assessment should be performed at least daily until symptoms resolve to baseline. In addition, brain imaging should be considered.
- Subjects with new onset Grade ≥ 2 neurologic symptoms post-KTE-X19 infusion will have a LP performed to evaluate for potential causes.

d **ECHO/MUGA/Chest CT/MRI**: See Section 7.6 for details.

e **CT or MRI disease assessment (Section 7.8.1)**: Diagnostic quality contrast-enhanced (unless contraindicated) CT (preferred) or MRI of the head, neck, chest, abdomen and pelvis must be performed within 28 days before enrollment to confirm eligibility. Scans obtained as part of SOC before signing of the informed consent form and within 56 days can be used for eligibility. If the subject received treatment for CLL or SLL after the eligibility images were obtained, then additional baseline images must be taken after the completion of CLL/SLL treatment and within 28 days before conditioning chemotherapy. CCI [redacted] Additional images should be performed per the SOA and at any time disease progression is suspected. CT Head tumor assessments to be done as clinically indicated, post-Screening. CT Head imaging not required at every visit.

f **LDH/Ferritin/CRP monitoring:** CRP should be collected daily while hospitalized for the KTE-X19 infusion and for subsequent hospitalization for a KTE-X19 related AE. If subject develops CRS or neurological symptoms, LDH and Ferritin should be monitored.

g **Lumbar puncture/CSF (Section 7.7):** Subjects with new onset Grade ≥ 2 neurologic symptoms post-KTE-X19 infusion will have a LP performed to evaluate for potential causes. A portion of the CSF will be submitted to the central lab for evaluation of KTE-X19 levels and cytokines.

h **Bone marrow aspirate and biopsy (Section 7.8.2):** CCI [redacted] CCI [redacted] Bone marrow evaluation should be considered for persistent cytopenias and to diagnose HLH if appropriate. A bone marrow evaluation should be performed at the time of progressive disease.

i [redacted]

j **Blood draw for anti-KTE-X19 antibodies:** Baseline antibody samples to be collected prior to start of leukapheresis. If positive at Month 3, additional samples will be collected every 3 months until titers return to baseline, are negative, or up to 12 months post-KTE-X19 infusion

k **Blood draws for PBMCs and cytokines**: During the observation period, PBMCs will be collected on Day 7 and cytokines will be collected on Day 1, 4, and 7.
- Following the initial hospitalization for the KTE-X19 infusion, if the subject is hospitalized with any KTE-X19 related adverse events, blood samples for PBMCs and cytokines will be collected on day of admission, then weekly, and on day of discharge.
- If the subject experiences a Grade ≥ 3 KTE-X19-related toxicity, such as Grade 3 CRS or neurologic event, one additional blood draw for cytokines will be taken at the time of the Grade ≥ 3 KTE-X19-related toxicity and upon resolution of the event.
- If the subject experiences a Grade >/= 2 CRS (per Lee 2014 criteria), an additional cytokine sample should be drawn at the first onset and first reoccurrence of any ≥ grade 2 CRS if not already collected on that day.
- PBMC collection will continue after subject experiences disease progression but remains on study

l **Viral testing for EU sites:** For EU sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations. Testing may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.

m **AE/SAE reporting (Sections 9.2 and Section 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 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 SAE 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.

n **Concomitant medications reporting (Section 6.2):** 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.

o **Subsequent therapy for CLL/SLL (Section 6.4):** Documentation of subsequent therapy for CLL/SLL will continue to be documented while the subject remains on study. Subjects may be contacted by telephone.

p **Survival Status (Section 7.14):** Subjects may be contacted by telephone to confirm survival status.

q **KTE-X19 Administration Period:** refer to Appendix 4 for requirements by country regulatory agencies.

r **Pregnancy test (serum or urine)**: **EU only:** test to be completed within 7 days prior to both Leukapheresis and Conditioning Chemotherapy for females of childbearing potential.

s After completion of at least 3 months of assessments in the KTE-C19-108 study, subjects who received an infusion of KTE-X19 will be provided the opportunity to transition to a LTFU study (KT-US-982-5968) after providing signed informed consent, to complete the remaining time of their 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 while continuing 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 the IP, study treatment, or other protocol-required therapies and must also 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.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol-required therapy, undergo procedures, and continue participating in study follow-up. Subject data collected up until withdrawal of consent will be retained and included in the analysis of the study. Publicly available data (death records) can be included after withdrawal of consent if local regulations permit. 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 also be asked to 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 IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol-required IP or procedures include any of the following:

- AEs
- 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. Definition of Adverse Events

An AE 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 AE(s) observed by the investigator or reported by the subject are recorded in the subject's medical record. The definition of AE 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 AE.

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

The term "disease progression," as assessed by measurement of malignant lesions on radiographs or other methods, should not be reported as AEs. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, CLL).

When an AE or SAE is due to the disease under investigation, it is necessary to report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as AEs in the appropriate section of the CRF.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. If a subject requests to withdraw from protocol-required therapies or the study because of an AE, then the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.1.1. Diagnosis Versus Signs and Symptoms

For AEs, 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 AE. A vital sign result must be reported as an AE 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 AE. 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 AE 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:

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, CCI CSF prophylaxis, conditioning chemotherapy) or until initiation of a new anticancer 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 serious adverse events. See Section 9.4 for reporting requirements.

See Section 6.2 for concomitant medication and Section 9.4 for SAE reporting requirements.

The investigator must provide the information listed below regarding the AEs being reported:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to IP, conditioning chemotherapy, or study procedures
- Action taken

The AE grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov). CRS events will be reported using the grading scale outlined in the IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to KTE-X19, CCI conditioning chemotherapy, any protocol-required study procedure or treatment, disease progression, concurrent disease, concomitant medication, or other. 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 AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.

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

9.3. Definition of Serious Adverse Events

An 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
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

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.

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 AE 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 AE recorded on the eCRF.

Disease progression of the malignancy is not considered an AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and indicated as being due to disease progression with the CRF. If the malignancy has a fatal outcome before the end of the SAE reporting period, then the event leading to the death must be recorded as a SAE with the outcome being fatal.

9.3.1. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE as described in Section 9.4.

The following hospitalization scenarios are not considered to be serious adverse events:

- 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 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 the table below, all SAEs will be reported within 24 hours and recorded in the CRF.

Table 6. Reporting Requirements for Serious Adverse Events

Subjects who screen-fail or who are enrolled, but do not receive KTE-X19 infusion	**Subjects who are enrolled and receive KTE-X19 infusion**
SAEs that occur from signing of the informed consent form through 30 days after the last study specific procedure (eg, screening procedure, leukapheresis, CCI conditioning chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first, will be recorded in the CRF	• All SAEs that occur from signing of the informed consent form through 3 months after the KTE-X19 infusion or until initiation of another anticancer therapy, whichever occurs first • After 3 months, only targeted SAEs will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first ○ 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 serious adverse events from the time the SCT preparative regimen commences through 24 months after KTE-X19 infusion or disease progression, whichever occurs first • All SAEs deemed related to KTE-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

See Section 6.2 for concomitant medication and Section 9.2 for targeted AE reporting requirements.

All SAEs must be submitted to Kite via the eSAE system within 24 hours of the investigator's knowledge of the event. If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the SAE Report Form and emailed to the SAE Reporting mailbox: PPD .

Subsequently, all SAEs will be reported in accordance with the EU guidelines, or if applicable, as per local reporting guidelines.

Following completion of KTE-C19-108, any relevant information regarding ongoing SAEs must be submitted to Kite Pharma within 24 hours of the investigator's knowledge of the event using the hardcopy format SAE Report Form and sent via e-mail to the SAE Reporting mailbox: PPD .

9.5. 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. The term "unexplained death" should be captured if the cause of death is not known. However, every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy). Deaths during the post-study survival follow-up due to underlying cancer should be recorded only on the Survival Status CRF.

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. Refer to Appendix 5 for complete list of highly effective contraception methods.

Any pregnancy in a female subject enrolled into the study must be reported, regardless of the time after KTE-X19 infusion. If a pregnancy occurs in either a female subject enrolled into the study or a female partner of a male subject within 6 months of completing conditioning chemotherapy or the administration of KTE-X19, 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 the sponsor.

Pregnancy Report Forms should be reported to Kite Patient Safety and Pharmacovigilance at PPD or fax: PPD.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (eg, a spontaneous abortion, an 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 the 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.

Pregnancies of female partners of male study subjects exposed to KTE-X19 or other study drugs must also be reported, and relevant information should be submitted to Kite Patient Safety and Pharmacovigilance using the pregnancy and Pregnancy Outcome Report Form within 24 hours. 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 while the female subject is taking protocol-required therapies, 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 long-term follow-up period. Report the lactation case and Special Situations Reporting Forms to Kite Patient Safety and Pharmacovigilance at PPD or fax: PPD.

Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

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 during the Phase 1 component of the study and make recommendations on further study conduct and progression of the study based on all data available, including the incidence of KTE-X19 DLT, review of SAEs, and cell expansion of KTE-X19. The SRT safety review outcome will be communicated to the active clinical study sites after the SRT safety review meeting.

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

Table 7. DLT Criteria

DLT	Exceptions
All KTE-X19-related Grade 3 non-hematologic toxicities lasting for > 7 days	• 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
All KTE-X19-related Grade 4 non-hematologic toxicities regardless of duration	
Grade 4 hematologic toxicity lasting more than 30 days if not attributable to underlying disease	Lymphopenia

CRS will be graded according to a revised grading system {Lee 2014}. AEs 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.

A 6 + 3 dose escalation/de-escalation plan was used in the initial Phase 1 DLT evaluation period, Cohort 1 and Cohort 2. Cohort 3 will enroll and dose 3 subjects at a dose of $1x10^6$ anti-CD19 CAR T cells/kg. This is an exploratory cohort. No additional dose levels will be evaluated.
A 3 + 3 design will be used for Cohort 4 SRT evaluation. The initial target dose to be evaluated will be 1×10^6 anti-CD19 CAR T cells/kg (Starting Dose). An additional target dose that may be evaluated in Cohort 4 is 2×10^6 anti-CD19 CAR T cells/kg (Escalation Dose). Escalation to a dose cohort will depend on review of all data available including the number of DLTs within a dose cohort among DLT-evaluable subjects (see Section 10.6). Three to 12 subjects will be enrolled and dosed in Cohort 4. If ≤1 subjects develops a DLT, enrollment will continue to Cohort 4 Escalation Dose. The following table provides details for the dose escalation/de-escalation plan based on the incidences of DLTs for Cohort 1 and Cohort 2.

Table 8. DLT Evaluation Cohort 1 and Cohort 2

Dose Cohort 1 and 2	If incidence of DLT*	Then
1 x 10^6 anti-CD19 CAR T cells/kg (initial dose) (Dose Level 0)	< 2 out of 6	Proceed to Dose Level 1 (2 x 10^6 anti-CD19 CAR T cells/kg)
	= 2 out of 6	enroll 3 more subjects at current dose (Dose Level 0)
	< 3 out of 9	Proceed to Dose Level 1 (2 x 10^6 anti-CD19 CAR T cells/kg)
	≥ 3	Proceed to Dose Level -1 (0.5 x 10^6 anti-CD19 CAR T cells/kg)
0.5 x 10^6 anti-CD19 CAR T cells/kg (Dose Level -1)	< 2 out of 6	Dose Level -1 is the MTD
	= 2 out of 6	Enroll 3 more subjects at current dose (Dose Level -1)
	< 3 out of 9	Dose Level -1 is the MTD
	≥ 3	Additional dose levels lower than Dose Level -1 may be explored
2 x 10^6 anti-CD19 CAR T cells/kg (Dose Level 1)	< 2 out of 6	Dose Level 1 is the MTD
	= 2 out of 6	Enroll 3 more subjects at current dose (Dose Level 1)
	< 3 out of 9	Dose Level 1 is the MTD
	≥ 3	Dose Level 0 is the MTD

The following table provides details for the dose escalation plan based on the incidences of DLTs for Cohort 4.

Table 9. DLT Evaluation Cohort 4

Dose Cohort 4	If incidence of DLT*	Then
1 x 10^6 anti-CD19 CAR T cells/kg (initial dose) (Dose Level 0)	0 out of 3	Proceed to Dose Level 1
	1 out of 3	Enroll 3 more subjects at current dose (Dose Level 0)
	> 1 out of 3 or > 1 out of 6	No MTD is found for cohort 4
	1 out of 6	Proceed to Dose Level 1
2 x 10^6 anti-CD19 CAR T cells/kg (Dose Level 1)	0 out of 3	Dose Level 1 is the MTD
	1 out of 3	Enroll 3 more subjects at the current dose level (Dose Level 1)
	> 1 out of 3 or >1 out of 6	Dose Level 0 is the MTD
	1 out of 6	Dose Level 1 is the MTD

Abbreviations: DLT, dose limiting toxicities; MTD, maximum tolerated dose
*DLT evaluable subjects

For the safe dose level identified, additional subjects will be enrolled and dosed so that the cohort will have up to 9-12 subjects to further evaluate the safety profile.

9.8. Criteria to Pause Enrollment

Study enrollment will be paused in Phase 1 following any grade 5 adverse event that occurs within 30 days of KTE-X19 infusion regardless of attributions.

In the event that the enrollment is paused after the pausing criteria have been met, overall assessment of the benefit/risk ratio will be conducted. If the overall assessment of the benefit/risk ratio is favorable, the study can resume enrollment. Restart of the study may require prior approval if required by applicable regulatory requirements or mandated by in country Regulatory Agency (see Appendix 4).

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

No formal hypothesis testing for this phase 1 study.

10.2. Study Endpoints

10.2.1. Primary Endpoints

Incidence of DLTs in subjects treated with KTE-X19 (Section 9.7)

10.2.2. Secondary Endpoints

- Incidence of AEs
- Levels of anti-CD19 CAR T cells in blood
- Overall Response Rate (ORR): The incidence of a CR, CRi, or PR per investigator review as defined by IWCLL 2018 criteria (Appendix 3).

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

10.3. Sample Size Considerations

For Cohort 1 and Cohort 2, the study enrolled and dosed a total of 9 subjects with no DLT observed. The anticipated enrollment for Cohort 3 and Cohort 4 is up to approximately 18 subjects, leaving the total up to 27 subjects enrolled and dosed in this study.

Cohort 3 will enroll and dose 3 subjects in an exploratory cohort. No additional subjects will be enrolled or dose levels evaluated.

Cohort 4, the SRT will review all data available including safety and efficacy data after 3 to 6 subjects enrolled and dosed at each dose level (see Section 10.6) have had the opportunity to be followed for 28 days after the KTE--X19 infusion. If the lymphodepleting regimen and one or more KTE-X19 doses evaluated in Phase 1 are determined to be safe based on all data available, including overall safety profile, the incidence of DLT, and cell expansion of KTE-X19, up to approximately total of 12 subjects may be enrolled and dosed in the dose cohort to further evaluate safety. The maximum number of subjects, including those enrolled and dosed in Cohort 4 will be approximately 15 subjects.

10.4. 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 for the study 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 plan, SRT charter, and Trial Integrity Document.

10.5. Interim Analysis and Early Stopping Guidelines

During the study, SRT meetings will review the safety and PK data after 3-6 subjects had been dosed at the level of 1 x or 2 x 10^6 anti-CD19 CAR T cells/kg and followed for 28 days.

The SRT will review the safety data and make recommendations on further study conduct and progression of the study as outlined in Section 9.7.

The sponsor reserves the right to conduct additional analyses of safety and efficacy for regulatory interaction purposes. If conducted, no formal hypothesis testing will be performed in such analyses.

10.6. Analysis Subsets

DLT-evaluable set: All subjects treated with the target KTE-X19 dose and followed for at least 28 days, or who 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 analysis set is defined as all subjects treated with any dose of KTE-X19.

Full analysis set (FAS): The full analysis set will consist of all enrolled subjects and may be used for the summary of subject disposition and subject listings of deaths.

Modified intent-to-treat (mITT) set: The modified intent-to-treat set will consist of subjects enrolled and treated with KTE-X19 and with radiographically measurable disease CCI [redacted] prior to administration of conditioning chemotherapy. CCI [redacted]

10.7. Planned Method of Analysis

All the analyses will be descriptive. The final analysis will occur when all subjects have completed the study.

10.7.1. ORR

The incidence of objective response and exact 2-sided 95% confidence intervals will be generated.

CCI [redacted]

[redacted]

CCI [redacted]

10.7.8. Safety

Subject incidence rates of treatment-emergent adverse events (TEAEs), defined as adverse events with onset on or after the KTE-X19 infusion, will be summarized. TEAEs including all, serious, fatal, CTCAE version 5.0 Grade 3 or higher and treatment-related AEs 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.

11. REGULATORY OBLIGATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

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 Independent Review Board /Independent Ethics Committee (IRB/IEC) for approval. After 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 SAEs (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 maintained within all material that is submitted to the key sponsor contact. The following rules are to be applied.

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

For reporting of SAEs, subjects will be identified by their respective subject identification number, initials, and year of birth (as per their local reporting requirements for both initials and year of birth).

Per country-specific regulations and ICH/GCP guidelines, investigators, and institutions are required to permit authorization to the sponsor, Contract Research Organization (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, Inc. under the following criteria:

- Is 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 investigator's 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, Inc. and the investigator reserve the right to terminate the investigator's 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 regarding either the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma, Inc. reserves the unilateral right, at its sole discretion, to determine whether to manufacture KTE-X19 and provide it to sites and subjects after the completion of the study.

13. STUDY DOCUMENTATION AND ARCHIVING

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. The 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. Examples of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology 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, the use of the CRFs as source documentation is not recommended as a routine practice.

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

- Subject content including ICFs and subject identification lists
- Protocols and protocol amendments, Investigator's 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, Inc. and the investigator. If storage is no longer available to archive source documents, or if source documents must be moved to an alternative location, the research staff should notify the key sponsor contact prior to 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 must also assure that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence and 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 (Study Documentation and Archive).

By signing the investigator's 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 therapies should be identified by tradenames. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in ZUMA-8 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 that 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, Inc. for review and approval. The study contract among the institution, principal investigator, and Kite Pharma, Inc. or its delegate will outline the requirements for publication review.

16. COMPENSATION

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

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VENCLEXTA, AbbVie Inc. VENCLEXTA® (venetoclax tablets) for Oral Use. U. S. Prescribing Information. North Chicago, IL. Revised: July. 2019:

ZYDELIG, Gilead Sciences Inc. ZYDELIG® (idelalisib) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised: September. 2016:

18. APPENDICES

Appendix 1. Sponsor and Investigator Signature Page

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGMENT

A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Amendment 3.0, 01 September 2021

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

PPD

DocuSigned by:
PPD

Kite Medical Monitor Name (Printed)

Signature

September 9, 2021 | 12:17:52 AM PDT

Date

INVESTIGATOR STATEMENT

I have read the 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 the 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 the 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)
- Subinvestigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to one 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

Appendix 2. Binet and Rai Staging Systems for the Classification of CLL

Binet

Stage	Lymph Node Areas	Hemoglobin < 10 g/dL	Platelet < 100 × 10^9/L
A	< 3	No	No
B	≥ 3	No	No
C	±	Either present	

Rai

Stage	Lymphocytosis	Lymph Node Enlargement	Spleen/Liver Enlargement	Hemoglobin < 11 g/dL	Platelet < 100 × 10^9/L
0	Yes	No	No	No	No
I	Yes	Yes	No	No	No
II	Yes	±	Yes	No	No
III	Yes	±	±	Yes	No
IV	Yes	±	±	±	Yes

Appendix 3. IWCLL 2018 Response Criteria and Disease Response Assessment

The determination of CLL response and progression will be based on standardized International Workshop on CLL (IWCLL) 2018 criteria. These criteria will be used to assess SLL.

Appendix Table 1. IWCLL 2018 Response Criteria

Parameter	CR	PR	PD
Group A (indicating tumor load)			
Lymphadenopathy[1]	none ≥ 1.5 cm	decrease ≥ 50%	increase by ≥ 50% or new lymph nodes ≥ 1.5 cm
Hepatomegaly	none	decrease ≥ 50%	Increase by ≥ 50 %
Splenomegaly	none	decrease ≥ 50%	Increase by ≥ 50 %
Blood lymphocytes	< 4000/µL	decrease of ≥ 50% from baseline	Increase by ≥ 50% over baseline[2] to ≥ 5000/µL
Group B (indicating function of the hematopoietic system)			
Platelet count	≥ 100,000/µL	≥ 100,000/µL or increase by ≥ 50% from baseline	Decrease by ≥ 50% from baseline due to CLL
Hemoglobin	≥ 11 g/dL	≥ 11 g/dL or increase by ≥ 50% from baseline	Decrease by ≥ 2 g/dL
Bone Marrow	Normocellular for age, no increase in CLL lymphocytes, no clonal B-lymphoid nodules[3]	CLL cells or clonal B-lymphoid nodules present	Increase in CLL cells by ≥50% on successive biopsies

1 Assessed as sum of the products of up to 6 lymph nodes
2 Subjects with treatment-related lymphocytosis should not be rated PD and remain on study treatment if other criteria for progressive disease are absent.
3 In case of B-lymphoid nodules assessment is recommended to clarify if the population is clonal—if not, subjects can be assessed as CR/CRi if all other criteria are fulfilled.

Appendix Table 2. Disease Response Assessment

Overall Disease Response	Criteria in Appendix Table 1	Additional Criteria
CR	All criteria in Group A and B	No disease related symptoms should be present, neutrophil count ≥ 1500/μL
CRi	All criteria for CR are met except with platelet count <100,000/μl, hemoglobin < 11 g/dL or neutrophil count < 1500/μL	
PR[1]	At least 1 criteria from Group A and 1 from Group B must be fulfilled.	If only one criterion is abnormal at baseline from Group A or B, only that criterion must improve.
SD	Failure to achieve a PR and absence of PD	
PD	Presence of at least 1 of the criteria from Group A or Group B	Constitutional symptoms alone do not define PD. A bone marrow biopsy should be performed to confirm progression if blood count changes are the only evidence of progression.

1 Nodular PR is defined as a CR/CRi with the presence of nodules of clonal lymphocytes in the bone marrow and will be considered a PR for the purposes of this study.

CCI

[redacted]

Appendix 4. Country specific regulatory agency requirements

France and Italy

The post-infusion monitoring of subjects, described in Section 7.9.3.2.2. of this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 3, column “KTE-X19 Administration Period, D1 to 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 7.5), blood draw for chemistry panel with CRP, blood draw for CBC w/differential, and neurological assessment (see Section 7.7). Any observed toxicity will be managed according to Section 7.10 of this protocol.

Germany

The post-infusion monitoring of subjects, described in Section 7.9.3.2.2. of this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 3, column "KTE-X19 Administration Period, D 1 to 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 7.5), blood draw for chemistry panel with CRP, blood draw for CBC w/differential, and neurological assessment (see Section 7.7). Any observed toxicity will be managed according to Section 7.10 of this protocol.

Appendix 5. Birth control methods which may be considered as highly effective[1]

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[2]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[2]:
  - oral
  - injectable
  - implantable[3]
- intrauterine device (IUD)[3]
- intrauterine hormone-releasing system (IUS)[3]
- bilateral tubal occlusion[3]
- vasectomized partner [3,4]
- sexual abstinence[5]

1 2014 clinical trial facilitation and coordination group contraception guidance
2 Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method
3 Contraception methods that in the context of this guidance are considered to have low user dependency.
4 Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success
5 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.