CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1 Open-label, Multicenter Study Evaluating the Safety of KITE-222, an Autologous Anti-CLL-1 CAR T-cell Therapy, in Subjects With Relapsed/Refractory Acute Myeloid Leukemia
Protocol Number:	KT-US-486-0201
Indication:	Relapsed/refractory acute myeloid leukemia
Kite Investigational Product:	KITE-222
Kite IND Number:	27115
EudraCT Number:	2020-000962-40
Clinical Trials.gov Identifier:	NCT04789408
Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Contact Information:	The medical monitor's name and contact information will be provided on the Key Study Team Contact List

Protocol Version/Date:	Original:	20 April 2020
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Kite Pharma, Inc.
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Study Title:	A Phase 1 Open-label, Multicenter Study Evaluating the Safety of KITE-222, an Autologous Anti-CLL-1 CAR T-cell Therapy, in Subjects With Relapsed/Refractory Acute Myeloid Leukemia
Indication:	Relapsed/refractory (r/r) acute myeloid leukemia (AML)
Investigational Product:	KITE-222
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	27115 2020-000962-40 NCT04789408
Number of Study Sites Planned:	Approximately 15 study sites in the United States and European Union
Objective:	Evaluate the feasibility, safety, maximum tolerated dose (MTD), and optimal dose of KITE-222 in the treatment of subjects with r/r AML
Endpoints:	Primary • Incidence of dose-limiting toxicities (DLTs) in subjects treated with KITE-222 Secondary • Incidence of adverse events (AEs) • Clinically significant changes in laboratory parameters • Time to neutrophil recovery • Time to platelet recovery • Composite complete remission (CCR) rate, defined as the proportion of subjects who achieve a complete remission (CR) plus the proportion of subjects who achieve a CR without measurable residual disease ($CRMRD^-$) plus the proportion of subjects who achieve a CR with incomplete hematologic recovery (CRi) per the European Leukemia Net (ELN) 2017 Classification {Dohner 2017}, as determined by the study investigators

	• Overall remission (OR) rate (CR + CRMRD$^-$ + CRi + morphologic leukemia-free state [MLFS] + partial remission [PR]) per the ELN 2017 Classification {Dohner 2017}, as determined by the study investigators. • Relapse-free survival (RFS) • Allogenic stem-cell transplant (allo-SCT) rate • Event-free survival (EFS) • Overall survival (OS) • 30- and 60-day all-cause mortality • Pharmacokinetics: peak and area-under-the-curve (AUC) of KITE-222 chimeric antigen receptor (CAR) T cells in subjects with r/r AML treated with KITE-222 • Pharmacodynamics: peak and AUC of selected biomarkers in subjects with r/r AML treated with KITE-222 • Analysis of antibodies against the KITE-222 CAR
Study Design: Number of Subjects Anticipated to Be Enrolled; Number of Subjects Anticipated to Be Enrolled and Treated:	Study KT-US-486-0201 is a Phase 1, open-label, multicenter study evaluating the feasibility, safety, and tolerability of KITE-222, an autologous CAR T-cell therapy targeting C-type lectin-like molecule-1 (CLL-1), in subjects with r/r AML. Initially, the study will enroll subjects to dose-escalation cohorts; approximately 18 subjects with r/r AML will be treated in a 3 + 3 study design to determine the MTD of KITE-222. For more details on the 3 + 3 study design and study conduct, please refer to Section 3.2 Study Design. After the dose-escalation stage, the study will expand to open an expansion cohort and enroll and treat approximately 22 subjects at the MTD of KITE-222 determined by the safety review team (SRT). The expansion cohort will refine the understanding of the safety, tolerability, and preliminary efficacy of KITE-222. There will be an additional SRT review after approximately the first 6 subjects are treated and followed for 28 days in the expansion cohort. To be eligible for the study, subjects are required to be fit for allo-SCT and have an identified stem-cell donor prior

	to enrollment. Enrollment occurs at the commencement of leukapheresis for the manufacturing of KITE-222. During the KITE-222 manufacturing window, subjects deemed by investigators to require bridging therapy may be treated with CCI [redacted] Upon successful manufacturing, subjects will receive non-myeloablative lymphodepleting chemotherapy with cyclophosphamide and fludarabine from CCI [redacted] KITE-222 will be administered on Day 0. Subjects must be hospitalized from infusion (Day 0) until Day 14 at a minimum. From Day 14, subjects may be evaluated for discharge and considered for outpatient follow-up if toxicities have returned to Grade 1, have resolved, returned to baseline, or are deemed clinically insignificant by the investigator (eg, renal insufficiency that is improving). Assessments detailed in the schedule of assessments (SOA) (Table 10, Table 11, and Table 12) can be obtained on an outpatient basis, including complete blood count (CBC), if KITE-222-related Grade 4 neutropenia persists. Conditioning chemotherapy for allo-SCT may be initiated only after completion of the Day 28 disease response assessment at the discretion of the investigator and after consultation with the medical monitor. Allo-SCT may be used to rescue persistent KITE-222-related Grade 4 neutropenia or thrombocytopenia (see DLT Section 8.1.2) or to consolidate response in subjects treated with KITE-222. For study requirements, refer to the SOA. Overall: Up to approximately 40 subjects will be treated in the study, of whom up to approximately 18 subjects will be treated in the dose-escalation cohorts and 22 subjects in the expansion cohort.

Target Population:	Adults (≥ 18 years of age) with r/r de novo or secondary AML as defined by the ELN 2017 Classification {Dohner 2017}, excluding acute promyelocytic leukemia.
Duration of Treatment and Study Participation:	Subjects will receive 1 infusion of KITE-222. The duration of the study for individual subjects will vary depending on a subject's response to treatment, survival, and timing of the transition to a separate Kite Long-term Follow-up (LTFU) study. For a subject who completes participation in this study and also completes the LTFU period in the separate LTFU study, the entire duration of a subject's participation in both studies will be up to approximately 15 years from the time of the initial infusion of KITE-222. The need for prolonged follow-up is based on the CCI [redacted] need to understand and mitigate the potential risks of delayed onset AEs.
Diagnosis and Main Eligibility Criteria:	Please refer to protocol Section 4.2 Eligibility Criteria for complete eligibility criteria. Subjects must have r/r AML with morphological disease in the BM and/or peripheral blood prior to enrollment (ie, commencement of leukapheresis for the manufacture of KITE-222). Subjects are required to be fit for allo-SCT and have an identified stem-cell donor prior to enrollment.
Study Procedures/ Frequency:	Enrollment occurs upon leukapheresis of the subject's peripheral blood mononuclear cells (PBMCs) for the manufacturing of KITE-222. During the KITE-222 manufacturing window, subjects deemed by investigators to require bridging therapy may be treated with CCI [redacted] Upon successful manufacture of KITE-222, subjects will receive lymphodepleting chemotherapy with cyclophosphamide CCI [redacted] and fludarabine

	CCI [redacted] KITE-222 will be administered IV as a single infusion of CAR-transduced autologous T cells at the assigned dose on Day 0. At the discretion of the investigator and after consultation with the medical monitor, subjects may proceed to conditioning chemotherapy for allo-SCT to rescue persistent Grade 4 neutropenia or thrombocytopenia toxicity (see DLT Section 8.1.2) and/or to consolidate response after the Week 4 disease response assessments are completed. At specific time points as outlined in the SOA, subjects will undergo the following assessments/procedures: collection of informed consent, general medical history including previous treatments for AML, physical examination including vital signs and performance status, neurologic assessments, blood draws for CBC, chemistry panels, coagulation, cytokines, C-reactive protein, levels of KITE-222/pharmacokinetics, lymphocyte subsets, CCI [redacted] CLL-1 expression analysis, and immunogenicity, including monitoring antibodies against the KITE-222 CAR. Females of childbearing potential will undergo a urine or serum pregnancy test. Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), brain computed tomography (CT) scan or magnetic resonance imaging (MRI) in cases with a prior history of central nervous system [CNS] involvement by AML or clinical symptoms suggestive of neurological involvement, chest x-ray or CT or MRI scan, and BM aspirate and biopsy prior to enrollment and associated leukapheresis. Subjects with a history of CNS malignancy, leptomeningeal carcinomatosis, or symptoms of CNS malignancy will have lumbar punctures performed for the collection of cerebrospinal fluid at screening and after KITE-222 infusion if they experience clinically significant Grade 2 or higher immune-effector cell-associated neurotoxicity. Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and AEs and will have their disease assessed.

Investigational Product and Study Treatments; Dose and Mode of Administration:

KITE-222 is an autologous CLL-1-targeted CAR T-cell therapy. The KITE-222 treatment regimen includes lymphodepleting chemotherapy followed by IV administration of KITE-222.

Lymphodepleting chemotherapy consists of the following:

- Cyclophosphamide CCI [redacted]
- Fludarabine CCI [redacted]

KITE-222 will be administered on Day 0 as a single IV infusion at one of the following assigned dose levels:

Dose Cohort	Number of KITE-222 CAR T Cells[a,b]	
	Subject Weight < 50 kg	Subject Weight ≥ 50 kg
Dose-escalation Cohort 1	CCI [redacted]	
Dose-escalation Cohort 2		
Dose-escalation Cohort 3		
Expansion Cohort	The optimal dose for the expansion cohort will be determined by the SRT after completion of the dose-escalation part	

Abbreviations: CAR, chimeric antigen receptor; SRT, safety review team.

a CCI [redacted]
All doses are acceptable within 20% of the assigned dose.

b A subject may receive the highest dose manufactured if less than the targeted dose after discussion with the Kite medical monitor. Out-of-specification product may be administered in line with the local regulation both during dose escalation and expansion phase.

Additional doses beyond the current schema may be explored at the discretion of the SRT as necessary for subject safety and to achieve a therapeutic window.

Safety Review Team

The SRT, consisting of study sponsor representatives and including at least 1 active study investigator, will review safety data and make recommendations on further study conduct during the study.

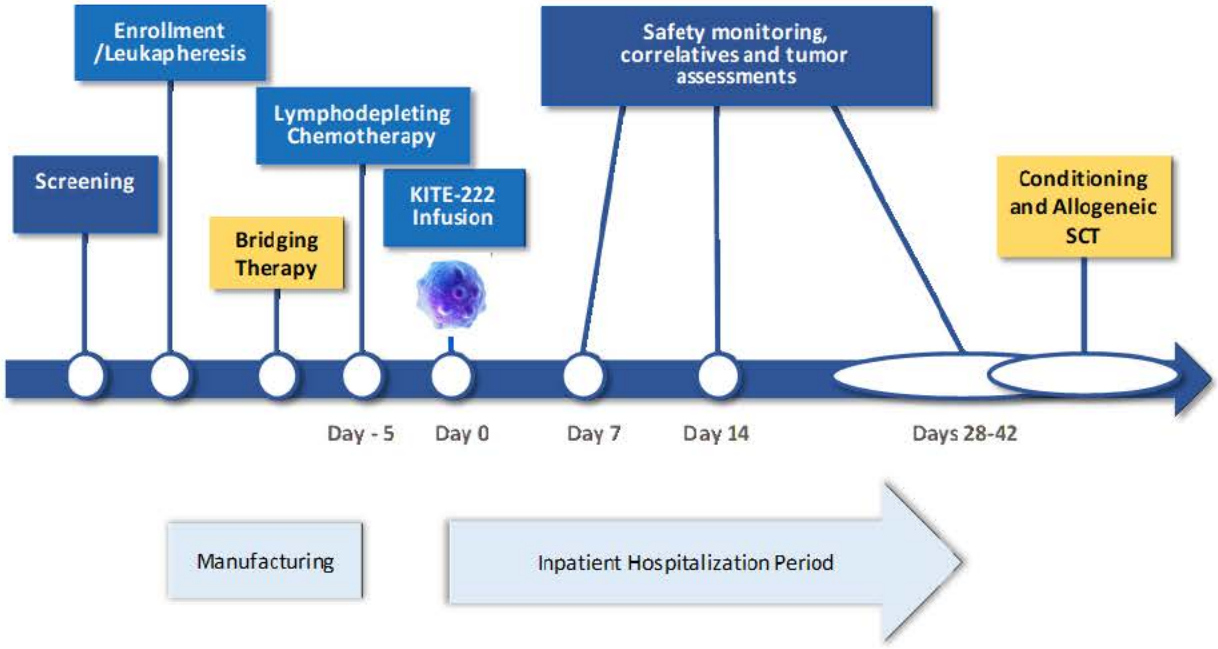
	The SRT will convene with a pause in treatment to confirm each dose escalation or de-escalation according to the 3 + 3 study design. The SRT will review safety data once the last treated subject of the 3 subject group has had the opportunity to be followed for 28 days and evaluated for the incidence of DLTs. During the expansion cohort, the SRT will convene to review AEs and serious AEs after approximately the first 6 subjects have had the opportunity to be followed for 28 days after administration of the optimal dose of KITE-222. Additional SRT meetings will occur as necessary through the course of the study to address safety concerns or other matters affecting study conduct.
Criteria for Evaluation:	Subjects will undergo assessments listed below according to the schedule presented in the SOA (Section 12.2).
Safety:	Safety assessments will include collection of AEs, clinical laboratory tests, physical examination, weight, vital signs, neurologic examinations, Eastern Cooperative Oncology Group (ECOG) performance status, cardiac function, brain MRI or CT (if MRI is not feasible), lumbar puncture, collection of concomitant medications, and assessment of the presence of anti-KITE-222 antibodies [redacted]
Efficacy:	Efficacy will be assessed in all subjects as a secondary endpoint. Disease response assessment will be performed as per ELN 2017 Classification (Section 12.5) {Dohner 2017}.
Pharmacokinetics/ Pharmacodynamics:	Pharmacokinetics and pharmacodynamics of KITE-222 will be assessed through samples sent to the central laboratory as per SOA. KITE-222 pharmacokinetics and pharmacodynamics will be reported as secondary endpoints.
Statistical Methods:	No formal hypothesis will be tested in this study. The study is designed to evaluate the feasibility, safety, and tolerability of KITE-222, an autologous CLL-1 targeted CAR T-cell therapy, in subjects with r/r AML. Demographic and baseline measurements as well as key safety and efficacy data will be summarized using standard descriptive methods.

	The primary analysis of the primary endpoint will be conducted when the last treated subject in the dose expansion cohort has had the opportunity to be evaluated for response 3 months after KITE-222 infusion or 1 month after allo-SCT, whichever occurs first.

This study will be conducted in compliance with this protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines of Good Clinical Practice including archiving of essential documents, and all applicable regulatory and local requirements.

This study will be conducted under United States Code of Federal Regulations Title 21 Part 312 or equivalent.

Figure 1. Study Schema



Subjects must be hospitalized from infusion (Day 0) until Day 14 at a minimum. From Day 14, subjects may be evaluated for discharge and considered for outpatient follow-up if toxicities have returned to Grade 1, have resolved, returned to baseline, or are deemed clinically insignificant by the investigator (eg, renal insufficiency that is improving). Assessments detailed in the SOA (Table 10, Table 11, and Table 12) can be obtained on an outpatient basis. including complete blood count (CBC), if KITE-222-related Grade 4 neutropenia persists.

Lymphodepleting chemotherapy: cyclophosphamide CCI fludarabine CCI

Bridging therapy as specified per protocol is CCI at the discretion of the treating investigator but it is highly recommended if CCI

CCI

LIST OF ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
Allo-SCT	allogeneic stem-cell transplant(ation)
AML	acute myeloid leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area-under-the-curve
Auto-SCT	autologous stem-cell transplant(ation)
BCL	B-cell lymphoma
BCMA	B-cell maturation antigen
β-hCG	beta-human chorionic gonadotropin
BM	bone marrow
CAR	chimeric antigen receptor
CBC	complete blood count
CCR	composite complete remission
CFR	Code of Federal Regulations
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CLL-1	C-type lectin-like molecule-1
CNS	central nervous system
CPF	cell processing facility
CR	complete remission
CRi	complete remission with incomplete hematologic recovery
$CRMRD^{-}$	complete remission without measurable residual disease
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DLBCL	diffuse large B-cell lymphoma
DLI	donor lymphocyte infusions
DLT	dose-limiting toxicity
DVT	deep vein thrombosis
eACT	Engineered Autologous T-cell Therapy™
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group

eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
ELN	European Leukemia Net
eSAE	electronic serious adverse event
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FLAG-Ida	fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor
FLT	fms-like tyrosine kinase
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVHD	graft-versus-host disease
HCP	health care provider
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HMA	hypomethylating agent
HSC	hematopoietic stem cell
IB	Investigator's Brochure
ICANS	immune-effector cell-associated neurotoxicity syndrome
ICE	immune-effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IDH	isocitrate dehydrogenase
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IL	interleukin
IND	investigational new drug
IP	investigational product
IPM	Investigational Product Manual
IRB	Institutional Review Board
ITD	internal tandem duplication
IUD	intrauterine device
IV	intravenous(ly)
KM	Kaplan-Meier
LDAC	low-dose cytarabine

LDH	lactate dehydrogenase
MCP-1	monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MFC	multiparametric flow cytometry
mITT	modified intent-to-treat
MLFS	morphologic leukemia-free state
MRD	measurable or minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NPM	nucleophosmin
OR	overall remission
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PO	orally
PR	partial remission
PT	preferred term
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
r/r	relapsed or refractory
CCI	[redacted]
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem-cell transplantation
SD	stable disease
SOA	schedule of assessments
SOC	system organ class
SRT	safety review team
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
US	United States
WBC	white blood cell

1. INTRODUCTION

1.1. Disease Background

1.1.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML), also known as acute myelocytic leukemia or acute myelogenous leukemia, is a heterogeneous hematologic malignancy that originates in myeloid precursors in the bone marrow (BM). Myeloid cells develop into subsets of leukocytes (granulocytes or monocytes, but not lymphocytes), erythrocytes, and thrombocytes. In AML, a patient's BM makes abnormal myeloblasts (blasts) that fail to differentiate. The accumulation of blasts and concomitant decrease in functional granulocytes, monocytes, erythrocytes, and thrombocytes leads to severe infections, anemia, and hemorrhage.

AML is the most common form of acute leukemia in adults, accounting for about a third of all leukemia diagnoses {National Cancer Institute (NIH) 2019, Sant 2014} and also represents the largest number of annual leukemia deaths in the United States (US) and Europe {National Cancer Institute (NIH) 2020, Sant 2014}. The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program estimates the occurrence of approximately 19,940 new diagnoses and 11,180 deaths from AML in 2020 in the US {National Cancer Institute (NIH) 2020}. The incidence, 4.3 per 100,000, is roughly equal across races and is substantially higher in men than women {Howlader 2020}. AML is generally a disease of older adults with a median age at diagnosis of 68 years; approximately 75% of patients are aged ≥ 55 years {Howlader 2019a, Howlader 2019b}. The 5-year overall survival (OS) rate for adults is 24% (67% for patients ≤ 19 years) in the most recently available analyses (2008 to 2014) in the US {American Cancer Society 2019}.

AML is a complex disease characterized by numerous somatically acquired mutations {Khwaja 2016}. For example, the Cancer Genome Atlas AML sub-study identified 23 genes that were commonly mutated (ie, recurrent mutations) {The Cancer Genome Atlas Research Network 2013}. The European Leukemia Net (ELN) recommendations for diagnosis and management of AML in adults classify AML into 3 major categories: AML with recurrent genetic abnormalities; AML with myelodysplasia-related changes; and AML, not otherwise specified {Dohner 2017}. The ELN category of AML with recurrent genetic abnormalities includes 11 categories, each with a defining genetic alteration. BM analysis with cytogenetics and/or fluorescent in-situ hybridization and molecular mutation analysis are typically performed to assess the risk and treatment options {O'Donnell 2017}.

Additional prognostic factors conferring an increased risk for poor outcome in AML include cigarette smoking and exposure to ionizing radiation {American Cancer Society 2019}. A large proportion of AML is secondary, arising from either chemotherapy (5% to 20%) or transformation of myelodysplastic syndromes and/or myeloproliferative neoplasms (10% to 20%) {Cheung 2019, O'Donnell 2017}. Patients diagnosed with secondary AML, regardless of the causative event, tend to exhibit worse clinical outcomes.

1.1.2. Current Treatment for Patients With AML and Unmet Need

Standard-of-care treatment for AML has evolved over the last decade with the advent of several targeted agents for specific AML subtypes and consideration of patient fitness for therapy over cutoffs by age. Broadly, subjects receive induction therapy to achieve remission, followed by consolidation therapy to deepen response {Dohner 2017}.

For eligible subjects, the backbone of therapy continues to comprise intensive chemotherapy to induce remission. Induction regimens have historically included a "7 + 3" regimen of cytarabine for 7 days plus an anthracycline (daunorubicin or idarubicin) or anthracenedione (mitoxantrone) for 3 days. Response rates to intensive induction chemotherapy are high, with 60% to 80% of younger adults and approximately 40% to 60% of older adults (> 60 years) achieving complete remission (CR) {Dohner 2017}. In recent years, some subjects with appropriate AML genetics may receive a tyrosine kinase inhibitor or anti-CD33 antibody-drug conjugate as part of their 7 + 3-based induction regimen. Achievement of remission is followed by consolidative chemotherapy, (typically 2 to 4 cycles of standard to high-dose cytarabine) to eliminate residual cancerous blasts {O'Donnell 2017}. A subset of patients with intermediate- to adverse-risk genetic abnormalities of AML in first or second CR may complete consolidation with allogeneic stem-cell transplantation (allo-SCT), or more infrequently, autologous stem-cell transplantation (auto-SCT) {Cerrano 2019, National Comprehensive Cancer Network (NCCN) 2018, O'Donnell 2017}. Approximately 3500 patients with AML annually receive an allo-SCT in US and almost 8000 in Europe according to the Center for International Blood and Marrow Transplant Research (CIBMTR) and European Society for Blood and Marrow Transplantation (EBMT) respectively. AML is the most frequent indication for allo-SCT and the number of patients receiving an allo-SCT has doubled in the last decade {Passweg 2020}.

Notably, patients considered ineligible for standard intensive induction chemotherapy regimens (based on performance status, comorbidities, cytogenetic/molecular abnormalities) have poorer outcomes and constitute the majority of patients with AML {Klepin 2014, O'Donnell 2017}. Treatment alternatives for this group of patients include best supportive care, low-intensity treatment, or clinical trials with investigational drugs. Low-intensity options include either low-dose cytarabine (LDAC) or therapy with a hypomethylating agent (HMA). LDAC is generally well tolerated with CR achieved in approximately 15% to 25% of subjects, but the OS is short at a median of 5 to 6 months. HMA regimens such as azacitidine have demonstrated an increased median OS of 10.4 months versus LDAC, best supportive care, and 7 + 3-based regimens, which showed a median OS of 6.5 months {Dombret 2015}. Recent Food and Drug Administration (FDA) approvals for treatment of elderly patients or who have comorbidities precluded from intensive induction chemotherapy include venetoclax in combination with HMAs (azacitidine or decitabine) or LDAC, and glasdegib in combination with LDAC {Huang 2019}. However, these newer regimens have not overcome the low CR rates or shortened median survival seen in patients unfit for intensive induction.

Despite the high response rates to induction therapy for fit subjects, relapsed disease is common even in this subset of patients {Dohner 2017, Hofmann 2019}. Moreover, approximately 25% of patients are refractory to intensive induction therapy {Othus 2015}. Patients with relapsed/refractory (r/r) AML have a short median OS of 3 to 9 months {Huang 2019, Sarkozy

2013, Short 2018, Stahl 2018}, and currently, no standard-of care-regimen exists for these patients (Table 1). Salvage therapies can include intermediate-dose cytarabine with or without anthracycline; fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-Ida); mitoxantrone, etoposide, and cytarabine. The aim of the treatment for fit subjects with r/r AML is to induce a complete response and consolidate with an allo-SCT {Dohner 2017, Jabbour 2014}. Several novel agents for the treatment of adult patients with r/r AML and targetable mutations have been approved by the FDA in the past few years, including enasidenib, ivosidenib, gemtuzumab ozogamicin, quizartinib, and gilteritinib {Cortes 2019, DiNardo 2018, Perl 2019, Stein 2019, Taksin 2007}. Despite the addition of these newly approved agents, clinical trial participation is still the first recommended option in r/r AML {Heuser 2020}, wherein additional novel therapies, including targeted immunotherapies, enzymatic inhibitors, and combination therapies, are currently being evaluated. However, much work is yet to be done for these to be translated into a substantial benefit for patients, as evidenced by the current 24% 5-year survival rate for adults with AML {American Cancer Society 2019}.

Table 1. Approved Regimens for the Treatment of Adults With R/R AML

Agent/ Reference	Description	Subjects	N	Median Age (Years)	CR/ CRi (%)	Subsequent Allo-SCT (%)	Median OS (Months)
Chemotherapy Regimens							
Clofarabine+ cytarabine 1 gm/m^2 {Faderl 2012}	Deoxyadenosine analog	r/r AML with ≤ 2 prior induction regimens	320	67	35/12	21	6.6
HDAC 1.5 gm/m^2 {Giles 2009}	Pyrimidine nucleoside	r/r AML in 1st relapse after prior CR/CRi	86	60	16/2	15	5.8
Investigator's choice of 7 cytarabine-containing regimens (MEC, FLAG-Ida, etc) {Roboz 2014}	Pyrimidine nucleoside	r/r AML after 2 or 3 prior induction regimens	190	60	12/9	11	3.3
CLAG-M {Wierzbowska 2008}	Purine analog, pyrimidine analog, and G-CSF	r/r AML	114	45	58/7	30 of subjects with CR	9.0
Azacitidine or decitabine {Stahl 2018}	Hypomethylating agents	r/r AML after ≥ 1 course of intensive chemotherapy	655	65	11/5	5.6	6.7
{Cortes 2015}	Liposome-encapsulated cytarabine and daunorubicin	First relapse after initial CR lasting ≥ 1 month	81	52	30/10	46	8.5

Agent/ Reference	Description	Subjects	N	Median Age (Years)	CR/ CRi (%)	Subsequent Allo-SCT (%)	Median OS (Months)
Targeted Agents							
Quizartinib {Cortes 2018}	FLT3 inhibitor	r/r AML with a FLT3-ITD activating mutation, after HSCT or one second-line salvage regimen	76	51 in cohort 2	4/40	35 in cohort 2	~5
Gilteritinib {Perl 2019}	FLT3 inhibitor	r/r AML after ≥ 1 induction	247	62	21/13	25	~6
Enasidenib {Stein 2017}	Inhibitor of mutant IDH	r/r AML with an IDH2[a] mutation	176	67	20/9	10	9.3
Ivosidenib {DiNardo 2018}	Inhibitor of mutant IDH	r/r AML with a susceptible IDH1[a] mutation	179	67	22/12	Not reported	8.8
Gemtuzumab ozogamicin {Taksin 2007}	Anti-CD33 mAb conjugated with calicheamicin (an anthracycline)	r/r $CD33^+$ AML	57	64	26/7	5	8.4
{DiNardo 2021}	BCL-2 inhibitor + FLAG-Ida	r/r AML	23	47	48/13	46	13
{Zappasodi 2021}	BCL-2 inhibitor + Hypomethylating agent	r/r AML with an available SCT donor	10	52	40/10	70	9

Abbreviations: allo-SCT, allogeneic stem-cell transplantation; AML, acute myeloid leukemia; BCL, B-cell lymphoma; CD, cluster of differentiation; CLAG-M, cladribine, ara-C, G-CSF, and mitoxantrone; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; FLAG-Ida, fludarabine, cytarabine, idarubicin, and G-CSF; FLT3, fms-like tyrosine kinase 3; G-CSF, granulocyte colony-stimulating factor; HDAC, high-dose cytarabine; HSCT, hematopoietic stem-cell transplantation; IDH, isocitrate dehydrogenase; ITD, internal tandem duplication; mAb, monoclonal antibody; MEC, mitoxantrone, etoposide, and cytarabine; OS, overall survival; r/r, relapsed/refractory; SCT, stem-cell transplantation
a. IDH1 and IDH2 are different isozymes of IDH.

For patients relapsing after allo-SCT the prognosis is poor. An analysis of the CIBMTR showed that of 1788 AML patients relapsing after allografts, only 23% of patients were alive at 1 year after relapse {Bejanyan 2015}. The 3-year OS increased as time from stem-cell transplant (SCT) to relapse increased, with estimates of 4%, 12%, 26% and 38% for relapses within 1 to 6 months, 6 months to 2 years, 2 to 3 years, and more than 3 years after allo-SCT, respectively {Dohner 2017}. There are currently no drugs specifically approved for this patient population. There are no apparent differences in survival between patients who receive donor lymphocyte infusions (DLI) and those that receive a second allo-SCT, with a 2-year survival rate of approximately 25% for both procedures. Non-relapse mortality is higher with the second allo-SCT than with DLI {Kharfan-Dabaja 2018}.

1.2. KITE-222

Kite Pharma, Inc. (hereafter referred to as Kite) is developing KITE-222, an autologous chimeric antigen receptor (CAR) T-cell therapy, targeting C-type lectin-like molecule-1 (CLL-1)[1]. CLL-1

[1] CLL-1 is also known as C-type lectin domain family 12 member A, myeloid inhibitory C-type lectin-like receptor, and dendritic cell-associated lectin 2.

expression is restricted to the surface of myeloid cells in peripheral blood and BM and is upregulated in AML (refer to Section 1.4.2).

Anti-CLL-1 CAR T cells are autologous human T cells that have been engineered to express an antibody-derived CCI fragment that recognizes CLL-1, combined with CCI Engagement of KITE-222 with CLL-1-expressing cells induces T-cell activation, expansion, production of cytokines, and targeted cytotoxicity.

The anti-CLL-1 CAR vector was designed, optimized and initially tested by Kite. Briefly, peripheral blood mononuclear cells (PBMCs) are obtained by leukapheresis CCI , and stimulated cells are transduced with a lentiviral vector containing an anti-CLL-1 CAR gene. Transduced T cells are then propagated in culture to generate sufficient engineered T cells for administration.

1.3. Summary of Relevant Nonclinical Studies With KITE-222

Nonclinical studies have demonstrated the in vitro and in vivo activity of KITE-222 against AML. Please refer to the current Investigator's Brochure (IB) for a summary on nonclinical data for KITE-222.

1.4. Study Rationale

1.4.1. Rationale for Study

As most advanced cancers eventually become refractory to conventional therapies, new treatment modalities are needed. Immunotherapy, which is based on enhancing an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Engineered Autologous T-cell Therapy™ (eACT™) is a process by which a patient's own T cells are collected and subsequently genetically altered to recognize and target antigens expressed on the cell surface of specific malignancies {Kochenderfer 2013}. The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies and has opened possibilities for the treatment of patients with a wide variety of cancer types.

Two recent CAR T-cell therapies developed by Kite Pharma, namely axicabtagene ciloleucel (axi-cel; YESCARTA®) and brexucabtagene autoleucel (brexu-cel; TECARTUS®), which are directed against the B-cell specific cell surface marker CD19, have resulted in clinically meaningful response rates in various B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and also B-cell acute lymphoblastic leukemia (ALL) {Jacobson 2022, Locke 2019, Neelapu 2017, Shah 2021a, Wang 2020}. Two additional anti-CD19 CAR T cell therapies have also been approved – tisagenlecleucel (KYMRIAH®) for DLBCL and ALL {Maude 2018, Schuster 2019, Schuster 2021}, and lisocabtagene ciloleucel (BREYANZI®) for DLBCL {Abramson 2020}. B-cell maturation antigen (BCMA) is a different antigen targeted by idecabtagene vicleucel (ABECMA®) and has also been approved for the treatment of multiple myeloma {Munshi 2021}.

KITE-222 is an autologous CAR T-cell therapy directed against CLL-1. Human CLL-1 is a 275-amino acid, type II transmembrane glycoprotein expressed in hematopoietic lineage cells, particularly in myeloid cell {Bakker 2004, Jiang 2018}. CLL-1 inhibits granulocyte and monocyte activity during inflammation, and may play a role in regulating both innate and adaptive immunity {Chiffoleau 2018, Han 2004, Ma 2019, Marshall 2004, Redelinghuys 2011}. CLL-1 is a promising target antigen for CAR therapy in AML because CLL-1 expression is restricted to the surface of myeloid cells, limiting off tumor toxicities to the hematologic compartment {Bakker 2004, Bill 2018, Chen 2006, Jiang 2018, Marshall 2006, Morsink 2019, van Rhenen 2007a, van Rhenen 2007b, Wang 2018}. As an autologous anti-CLL-1 CAR T-cell product, KITE-222 offers a promising approach to expand the scope of effective eACT to patients with AML.

1.4.2. Rationale for the Use of CLL-1 as a Target Antigen for AML

Human CLL-1 is a 275-amino acid, type II transmembrane glycoprotein expressed in hematopoietic lineage cells, particularly in myeloid cell {Bakker 2004, Jiang 2018}. CLL-1 inhibits granulocyte and monocyte activity during inflammation, and it may play a role in regulating both innate and adaptive immunity {Chiffoleau 2018, Han 2004, Ma 2019, Marshall 2004, Redelinghuys 2011}. CLL-1 is a promising target antigen for CAR therapy in AML, because CLL-1 expression is restricted to the surface of myeloid cells, limiting off-tumor toxicities to the hematologic compartment {Bakker 2004, Bill 2018, Chen 2006, Jiang 2018, Marshall 2006, Morsink 2019, van Rhenen 2007a, van Rhenen 2007b, Wang 2018}.

In previous studies, CLL-1 expression was found to be positive in 77% to 92% of patient samples by flow cytometry as defined by CLL-1 presence on > 20% of blasts; {Bakker 2004, Wang 2018}. Expression has been detected across AML French-American-British, morphological, and cytogenetic subtypes {Bakker 2004, Jiang 2018, Wang 2018, Zhao 2010}. Interestingly, CLL-1 is not only expressed in AML blasts, but also in hard-to-treat $CD34^+$ leukemic stem cells from patients with AML {Jiang 2018, van Rhenen 2007b}. Of note, in vitro non-clinical studies of KITE-222 have demonstrated target-specific killing of AML tumor lines that have a significant proportion of blasts with undetectable CLL-1 by multiparametric flow cytometry (MFC), including KG-1; please refer to the current IB for additional information.

Importantly, surface CLL-1 may be a safer target than alternate surface antigens evaluated in AML. CLL-1 has minimal to no expression on $CD34^+$ hematopoietic stem cells (HSCs); $CD34^+$ hematopoietic progenitors, erythrocytes, megakaryocytes, platelets, NK cells, B cells, T cells, or dendritic cells. Furthermore, CLL-1 is not expressed by normal BM $CD34^+CD38^-$ stem cells or by peripheral blood $CD34^+CD38^-$ cells mobilized with growth factors {Bakker 2004, Bill 2018, Chen 2006, Jiang 2018, Marshall 2006, Morsink 2019, van Rhenen 2007a, van Rhenen 2007b, Wang 2018}. Additionally, CLL-1 expression is limited to the myeloid compartment, with no expression detected in other organ tissue. Taken together, CLL-1 directed CAR T cells have promise to eliminate leukemic blasts and stem cells, without harming important HSCs, lymphocytes, or other organ tissues.

There have been several clinical experiences of treating AML with experimental drugs targeting CLL-1, including antibody-drug conjugates, bispecific antibodies, and chimeric-antigenic-receptors:

- DCLL9718S was an antibody-drug conjugate developed by Roche that was discontinued {Daver 2021}. Eighteen safety evaluable patients were assigned to 5 escalating dose level cohorts. The most common Grade 3 or higher adverse events (AEs) were febrile neutropenia (33%) and pneumonia (28%). No dose-limiting toxicities (DLTs) were reported. Based on 2 patients with Grade 3 hepatic events observed at the highest dose and lack of anti-leukemic activity, the dose escalation was stopped {Daver 2021}.
- MCLA-117 was a bispecific antibody developed by Merus Pharmaceuticals. Fifty-eight patients were treated across 11 dose levels and received a median of 5 infusions in a Phase I trial. Grade 3 or 4 cytokine release syndrome (CRS) and febrile neutropenia were reported in 8.6% and 5.2% of patients, respectively. No DLTs were observed. Further development was discontinued {Mascarenhas 2020}.
- A few trials have explored different constructs of autologous anti-CLL-1 CAR T cells, mainly in pediatric AML patients, and in some cases with multiple targets (Table 2).

Table 2. Clinical Trials Evaluating Anti-CLL-1 CAR T-cell Therapies in AML

Product / Sponsor / Trial	Construct	N / Median Age	Dose	Grade ≥ 3 AEs	Efficacy	Reference
4SCAR-CLL1 / Guangzhou Women and Children's Medical Center / NCT03222674	Different targets: CLL-1, Lewis-Y, CD33, CD38 CD28-CD27 costimulatory domain FKBP-caspase 9 switch-off	4 pediatric / 8.4 years	1-2 × 10^6/kg	No Grade ≥ 3 CRS or ICANS Three patients had prolonged Grade 4 neutropenia for 4 to 6 weeks	3 out of 4 patients achieved MRD negativity	{Zhang 2020, Zhang 2021b}
ICG144 / iCell Gene Therapeutics / NCT03795779	Biscistronic CLL1-CD28 and CD33-41BB	8 adults and 1 pediatric / 32 years	0.7-3.7 × 10^6/kg	CRS 2/9 ICANS 3/9 cytopenias 9/9	7 out of 9 MRD negative at 4 weeks	{Liu 2020}
BG1805 / Guangzhou Biogene Therapeutics ChiCTR1900027684	Two CAR-Ts: CLL-1-4-1BB or CLL1-CD33-4-1BB	11 pediatric / 12 years	0.35-1 × 10^6/kg	No Grade ≥ 3 CRS or ICANS cytopenias 11/11	6 out of 11 MRD negative at 4 weeks	{Zhang 2021a, Zhang 2022}
NCT04884984	PD-1 silenced CD28 OX40	2 adults / 28 years	5-10 × 10^6/kg with splitted dose	No Grade ≥ 3 CRS or ICANS Cytopenias 2/2	2 out 2 CRi MRD negative at 4 weeks	{Ma 2022}
ChiCTR2000041054	4-1BB 2nd generation	10 adults / 42 years	1–2 × 10^6 /kg	CRS 6/10 No ICANS observed 10/10 Cytopenias	7 out of 10 achieved CR/CRi at 4 weeks	{Jin 2022}

Abbreviations: AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL-1, C-type lectin-like molecule-1; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CRS, cytokine release syndrome; ICANS, immune-effector cell-associated neurotoxicity syndrome; MRD, minimal residual disease

1.4.3. Rationale for KITE-222 Starting Dose

Historically, there have only been few AML-directed cell therapies assessed in the clinical setting. In order to determine an initial starting dose and appropriate dose escalation for this study, it is important to evaluate both the AML-directed cell therapy landscape and experience from other CAR T-cell products.

Within AML-directed trials, no specific trial with published data represents an autologous approach similar to KITE-222; there is no US-based autologous anti-CLL-1 CAR T-cell trial to date {Budde 2017, Cellectis 2017}. However, initial data are available from a Phase I trial conducted in China evaluating safety of a dual-targeting CLL-1-CD33 CAR-T therapy {Liu 2020}. Nine subjects received conditioning chemotherapy with 3-day administration of cyclophosphamide (300 mg/m^2/day) and fludarabine (30 mg/m^2/day) followed by escalating doses of the CLL-1-CD33 CAR-T (starting dose 1×10^6 cells/kg up to 3×10^6 cells/kg). CRS was observed in the majority of subjects, with 2 of 9 patients experiencing Grade 3 CRS. Four patients developed neurotoxicity (3 patients with Grade 3 neurotoxicity). All subjects experienced Grade 4 pancytopenia and 3 subjects developed sepsis, 2 subjects developed fungal infections, and 3 subjects developed pneumonia. Efficacy was encouraging, as 7 of 9 subjects experienced measurable residual disease (MRD) negativity. Six of 7 responders proceeded to allo-SCT; 1 subject died of sepsis on Day 6 after allo-SCT. Overall, the study provides preliminary evidence of anti-leukemia activity of a dual-targeting CAR-T with no unexpected safety findings suggestive of on-target, off-tumor toxicity. It is important to note that CD33 is expressed on HSCs and targeting this antigen is thus expected to induce deep and durable cytopenias with risk of infectious complications. In contrast, KITE-222 only targets CLL-1, which is not expressed in HSCs, and thus has the potential for a more favorable safety profile. Another CAR T-cell therapy for AML with available data is MB-102, an anti-CD123 CAR T-cell product developed initially at the City of Hope {Budde 2017, ClinicalTrials.gov 2019a}. The treatment regimen for MB-102 utilizes standard conditioning chemotherapy followed by administration of MB-102. Dose escalation started with a flat dose of 50 million anti-CD123 CAR T cells that were well tolerated by 2 subjects; in the next dose level, subjects were treated with 200 million anti-CD123 CAR T cells. Subsequent studies with MB-102 have planned a flat dose of up to 600 million cells {ClinicalTrials.gov 2019c}. MB-102 has been manufactured in most published cases from donor-derived T cells in subjects who have already undergone allo-SCT from that donor {Budde 2017}.

UCART123 is another allogeneic product targeting CD123 that was initially studied at a dose of 6.25×10^5 anti-CD123 CAR T cells/kg, comparable in most subjects to the 50 million cells used as a flat starting dose in the MB-102 clinical study {Cellectis 2017, ClinicalTrials.gov 2019b}. Compared with the MB-102 study, the UCART123 study includes a more aggressive conditioning chemotherapy regimen that involves more days of fludarabine and higher doses of cyclophosphamide, possibly designed to prevent rejection of the allogeneic product {Graham 2018}. With the more intensive lymphodepleting chemotherapy administered in UCART123, Grade 5 CRS/capillary leak was observed at the starting dose of 6.25×10^5 CAR T cells/kg in a

subject with blastic plasmacytoid dendritic cell neoplasm and Grade 4 capillary leak was noted in the first subject treated with AML. The toxicities noted at the initial doses of UCART123 may have been exacerbated by on-target, off-tumor effects on endothelial cells, which express CD123 {Sun 2019}. Of note, CLL-1 is not known to be expressed in endothelial cells and thus, similar on-target, off-tumor toxicity is not expected.

Outside of AML, recent trials of autologous anti-CD19 and anti-BCMA CAR therapies also informed the initial dose selection and dose-escalation cohorts for this study of KITE-222. While anti-CD19 CAR T-cell therapy has used weight-based dosing, doses in the range of 60 to 100 million cells (approximately 1×10^6 anti-CD19 CAR T cells/kg) have been found to be safe in subjects across various B-cell malignancies including large BCL and acute lymphoblastic leukemia. CD19 is a particularly highly expressed target, and anti-CD19 CAR T cells have shown higher expansion and toxicity in the face of CD19-based activation {Neelapu 2017, Schuster 2019} than anti-BCMA CAR T-cell counterparts {Raje 2019}. Phase 1 experience with autologous anti-BCMA CAR T cells has demonstrated that flat dosing at 50 million cells or equivalent is a safe starting dose, and that DLTs may not be seen even at doses of up to 800 million cells for antigens other than CD19 {Brudno 2018, Raje 2019}. Dose-escalation cohorts across CAR T-cell therapy studies have typically been on the order of a half-log or 3-fold increase in the dose for initial cohorts, but up to a 4-fold increase from the initial dose has been tolerated {Budde 2017, Raje 2019}.

In conclusion, the starting dose proposed for KITE-222 CCI [redacted] is below the starting dose used for other CAR-T therapies in AML (CLL-1 CD33 CAR-T, MB-102, UCART123) as well as below starting doses applied for CD19- or BCMA-targeting CAR-T therapies. TheCCI dose-escalation steps are well aligned with the dose-escalation steps used in above Phase 1 CAR-T trials and aim at providing an optimal balance of benefit/risk.

1.4.4. Rationale for Trial Design to Address KITE-222 Safety Risk

Targeting CLL-1 may exacerbate prolonged neutropenia that can be seen in the setting of successful B-cell and plasma cell targeting CAR T-cell therapies {Neelapu 2017, Raje 2019, Schuster 2019}. Most notably, the expression pattern of CLL-1 within the myeloid compartment may lead to agranulocytosis. Although CLL-1 expression is low on normal $CD34^+$ common myeloid progenitor cells and megakaryocyte-erythroid progenitors, CLL-1 is expressed on the majority of granulocyte-macrophage progenitor cells, ranging from 62% to 81% CLL-1^+ cells by flow cytometry {Bill 2018}. These granulocyte-macrophage progenitor cells give rise to mature myeloid cells, including monocytes and granulocytes which typically express CLL-1 (98.1% and 99.6% of cells, respectively) {Bill 2018, Wang 2018}. The expression of CLL-1 across myeloid-lineage cells speaks to the risk of agranulocytosis, but this risk is felt to be manageable in the context of treating r/r AML subjects.

The risks of anti-CLL-1 CAR T-cell therapy with KITE-222 for agranulocytosis is felt to be mitigated by a few key features. First, as described in Section 1.4.2, CLL-1 is not present on HSCs. This is in contrast with other potential AML antigen targets for CAR T-cell therapy, such as CD33, CD123, and even fms-like tyrosine kinase (FLT)-3. Sparing HSC in the context of an

anti-CLL-1 CAR T-cell therapy may allow for the re-establishment of normal hematopoiesis in the weeks to months after anti-CLL-1 CAR T-cell infusion. Second, KITE-222 has been specifically designed with a CCI co-stimulation domain. The KITE-222 CCI co-stimulation is likely to decrease the persistence of anti-CLL-1 CAR T cells in KITE-222 versus other co-stimulation domains, CCI {van der Stegen 2015}. Finally, the intensive chemotherapy regimens used for r/r AML salvage therapy frequently result in Grade 4 neutropenia. These treatments are generally followed by allo-SCT to consolidate response in fit patients who had not previously undergone allo-SCT {Dohner 2017}. In this study, allo-SCT may be used to rescue persistent agranulocytosis and/or to consolidate response; therefore, subjects in this study will be required to have an identified stem-cell donor available before enrollment for prolonged neutrophil recovery.

1.4.5. Rationale for Bridging Therapy

Patients undergoing CAR T therapies often receive interim disease-directed therapy, referred to as bridging therapy, to maintain disease control and/or to prevent or treat progressive disease while awaiting CAR T cell manufacture and infusion {Amini 2022, Bhaskar 2022}.

Preliminary observations in KITE-222 (current study KT-US-486-0201) CCI . Similar findings have been described in other CCI CAR T therapies like brexucabtagene autoleucel or others in ALL {Curran 2019, Shah 2021a} or chronic lymphocytic leukemia {Brentjens 2011, Davids 2022}. Thus, debulking strategies in patients with high tumor burden could improve the efficacy and safety of CAR T therapies.

1.4.6. Rationale for Lymphodepleting Chemotherapy

Before receiving KITE-222, subjects will receive a nonmyeloablative lymphodepleting conditioning regimen consisting of cyclophosphamide CCI and fludarabine CCI to enhance anti-CLL-1 CAR T-cell function by creating an optimal environment for the expansion of KITE-222 in vivo. Subjects will receive lymphodepleting chemotherapy CCI

The use of lymphodepletion in this study is based on data from ZUMA-1, Kite's open-label, multicenter clinical study of the safety and efficacy of anti-CD19 CAR T cells in subjects with advanced forms of non-Hodgkin lymphoma {Locke 2017, Neelapu 2017}, an NCI trial of anti-CD19 CAR-T cells in subjects with advanced B-cell malignancies {Kochenderfer 2017}, earlier nonclinical publications that showed an association between adequate lymphodepletion and expansion, and function of adoptively transferred T cells in animal models {Dudley 2008, Gattinoni 2005}, and other reported experiences with autologous or allogenic anti-CD19 CAR-T therapies. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating regulatory T cells, or enhancing antigen-presenting cell activation {Amini 2022, Klebanoff 2005}. The proposed fludarabine dose is aligned with the approved use for axicabtagene ciloleucel and brexucabtagene ciloleucel in mantle cell lymphoma. The dose of cyclophosphamide was initially CCI in Dose Level 1 and Dose Level 2 of the current

protocol (through Amendment 3.0) to optimize expansion while minimizing the duration of hematopoietic recovery. After initial translational data suggested an inverse relation between tumor burden and expansion of cells in vivo, the dose of cyclophosphamide was increased to CCI [redacted]. Some trials in cell therapy have already administered higher doses of cyclophosphamide than in the ZUMA studies. Thus, Curran et al. found that high doses of cyclophosphamide (3 g/m^2) achieved better in vivo expansion of CAR T cells than patients receiving 1.5 mg/m^2 or lower in a trial with CCI [redacted] CAR T cells in ALL without increasing CAR T cell toxicity {Curran 2019}. In addition, a dose of 750 mg/m^2 of cyclophosphamide for 3 days is being used in similar CAR-T trials in progress, like UCART123 in BPDCN (NCT03203369), CYAD-211 (NCT04613557) in multiple myeloma, and PBCAR0191 (NCT03666000) in lymphoma {Shah 2021b}.

1.5. Benefit/Risk Assessment for the Study

KITE-222 is an autologous T-cell product, and to date, there are no nonclinical models to obtain relevant safety information. However, KITE-222 has demonstrated anti-tumor efficacy in nonclinical mouse models. Given the lack of suitable murine models to formally assess the safety of KITE-222 in a nonclinical setting, this Phase 1 clinical study will employ a gradual dose-escalation strategy with close safety review team (SRT) oversight.

Although we do not have data to date for the risks associated with KITE-222 in the clinical setting, the risks of other CAR T-cell therapies with other tumor targets have been well described, most notably for anti-CD19 CAR T-cell therapies. The identified risks of anti-CD19 CAR T-cell therapies include CRS and neurologic events of which severe and life-threatening events have occurred. Strategies have been developed for these AEs to monitor for early detection and management, and the rates of severe CRS and neurologic events have decreased as these therapeutic treatments have matured.

The advent of clinically efficacious immunotherapy for cancer over the last decade may represent a turning point in the care of subjects with advanced malignancies. Given the impact of myeloid cancers to the subject and the potential benefits considered in the context of potential risk, further development of KITE-222 in this study is justified.

Refer to the current IB for a summary of potential risks associated with KITE-222.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory and local legal requirements.

2. OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the feasibility, safety, maximum tolerated dose (MTD), and optimal dose of KITE-222 in the treatment of subjects with r/r AML.

2.2. Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the efficacy of KITE-222 in treating subjects with r/r AML
- To evaluate the pharmacokinetic and pharmacodynamic profiles of KITE-222 in subjects with r/r AML

CCI [redacted]

[redacted]

[redacted]

[redacted]

3. STUDY DESIGN

3.1. Endpoints

3.1.1. Primary Endpoints

The primary endpoint of this study is to evaluate the incidence of DLTs in subjects treated with KITE-222.

3.1.2. Secondary Endpoints

The secondary endpoints of this study are to evaluate:

- Incidence of AEs
- Clinically significant changes in laboratory parameters
- Time to neutrophil recovery
- Time to platelet recovery
- Composite complete remission (CCR) rate, defined as the proportion of subjects who achieve a CR plus the proportion of subjects who achieve a CR without measurable residual disease ($CRMRD^-$) plus the proportion of subjects who achieve a CR with incomplete hematologic recovery (CRi) per the ELN 2017 Classification {Dohner 2017}, as determined by the study investigators.
- Overall remission (OR) rate (CR + $CRMRD^-$ + CRi + morphologic leukemia-free state [MLFS] + partial remission [PR]) per the ELN 2017 Classification {Dohner 2017}, as determined by the study investigators.
- Relapse-free survival (RFS)
- Allo-SCT rate
- Event-free survival (EFS)
- OS
- 30- and 60-day all-cause mortality
- Pharmacokinetics: peak and area-under-the-curve (AUC) of KITE-222 CAR T cells in subjects with r/r AML treated with KITE-222
- Pharmacodynamics: peak and AUC of selected biomarkers in subjects with r/r AML treated with KITE-222

- Analysis of antibodies against the KITE-222 CAR

CCI [redacted]

3.2. Study Design

Study KT-US-486-0201 is a Phase 1, open-label, multicenter study evaluating the feasibility, safety, and tolerability of KITE-222 in subjects with r/r AML. The Phase 1 study will consist of dose-escalation cohorts and an expansion cohort. In the dose-escalation part, 3 dose cohorts will be assessed to determine the MTD using a 3 + 3 study design.

All subjects enrolled in the study will proceed through treatment as outlined in Figure 1 with the dose of KITE-222 determined according to dose-escalation cohort and by the MTD in the expansion cohort. CCI [redacted]. Subjects must be hospitalized from infusion (Day 0) until Day 14 at a minimum. From Day 14, subjects may be evaluated for discharge and considered for outpatient follow-up if toxicities have returned to Grade 1, have resolved, returned to baseline, or are deemed clinically insignificant by the investigator (eg, renal insufficiency that is improving). Assessments detailed in the schedule of assessments (SOA) (Table 10, Table 11, and Table 12) can be obtained on an outpatient basis, including complete blood count (CBC), if KITE-222-related Grade 4 neutropenia persists.

Subjects who enroll will have a pre-identified stem-cell donor source for potential allo-SCT, which can be initiated at the discretion of the investigating physician after completion of the Day 28 disease response assessment.

In the dose-escalation cohorts, the 3 + 3 design will be used to establish the MTD. In the 3 + 3 design, 3 subjects are initially treated in a given dose cohort. If there is no DLT observed in any of these subjects, the study proceeds to enroll additional subjects into the next higher dose cohort. If 1 subject develops a DLT at a specific dose, an additional 3 subjects are enrolled into that same dose cohort, and dose escalation is only suggested if no additional DLTs are observed

in this dose cohort. Development of DLTs in more than 1 subject in a specific dose cohort suggests the MTD has been exceeded, and further dose escalation is not pursued. The MTD is established when 6 subjects are treated at the highest dose level with < 2 DLTs.

An SRT, consisting of representatives of the study sponsor and at least 1 active study investigator, will review the safety data and make recommendations on study conduct during the dose-escalation part (Section 8.9). The SRT will meet to make decisions on the dose escalation during the 3 + 3 period and is responsible for establishing the MTD; as such, in certain circumstances, additional dose cohorts may be explored if KITE-222 is found to be safe at the highest dose level by the SRT.

The study starts with 3 subjects per dose-escalation cohort. After the first subject is enrolled in each cohort, the subsequent 2 subjects treated in that dose cohort will be enrolled 1 by 1, and dosing of each subject will occur only after the previous subject is clinically stable and has been monitored for at least 28 days after the KITE-222 infusion. Dosing subjects in the next cohort will require completion of the 28-day DLT window for the first 3 subjects treated and SRT confirmation of advancing the dose-escalation. Approximately 18 subjects will be enrolled for the dose-escalation part of this study, up to 6 subjects evaluable for DLT in each cohort. Once the evaluation of the dose-escalation cohorts is completed, the SRT will meet again to determine the MTD by reviewing the safety profile and other clinical data for subjects at all tested dose levels.

During the dose-escalation part, the SRT may adjust dose-escalation cohort dose levels to enhance safety before subject enrollment to said cohort, and after review of the safety data. Additional dose cohorts may be explored at the discretion of the SRT. Additional subjects treated at a new dose level suggested by the SRT may be added to the total subject number for the dose-escalation part.

After the MTD is established, the study will enter the expansion cohort stage and enroll and treat approximately additional 22 subjects to that cohort. A minimum of 28 subjects across the MTD-dose cohort and the expansion cohort will be treated for additional safety and preliminary efficacy assessments of the MTD determined by the SRT. After approximately the first 6 subjects are treated and followed for 28 days in the expansion cohort, the SRT will convene to assess the feasibility, safety, and preliminary efficacy of the MTD after the last treated subject completes the 28-day visit, including disease assessment.

The anticipated enrollment in this study should allow for having 40 subjects treated: up to 18 subjects for the 3 + 3 based dose-escalation part and approximately 22 subjects for the expansion cohort part.

3.3. Study Treatments

3.3.1. Leukapheresis

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells [WBCs]) for the manufacture of KITE-222 CCI [redacted] Leukapheresed cells obtained

from subjects at participating study sites will be packaged for expedited shipment to the cell processing facility (CPF) for the manufacture of KITE-222. Refer to Section 7.6.1 for more information about the leukapheresis procedure.

CCI [redacted]

[redacted]

CCI

CCI

[redacted]

CCI

CCI

[redacted]

3.3.3. Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy will be administered on Day −5 through Day −3 before administration of KITE-222 in order to induce lymphocyte depletion and create an optimal environment for the expansion of KITE-222 CAR T cells in vivo. Refer to Section 1.4.5 for additional information about the rationale for administration of lymphodepleting chemotherapy.

The lymphodepleting chemotherapy regimen will consist of cyclophosphamide CCI [redacted] and fludarabine CCI [redacted]

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent that also possesses potent immunosuppressive activity. Fludarabine phosphate is a synthetic purine antagonist antimetabolite.

Refer to Section 7.6.3 for details about the lymphodepleting chemotherapy procedures.

3.3.4. KITE-222 Dose Cohorts

KITE-222 will be administered as a single IV infusion at a target dose of KITE-222 CAR T cells per the assigned dose level cohort. Dose cohorts and dose levels are presented in Table 3. In the event that Dose-escalation Cohort 1 is found to be unsafe, the study will pause and the SRT will make adjustments to the treatment regimen to enhance safety (eg, a reduction in the intensity of the lymphodepleting chemotherapy and/or selection of the reduced dose for lower weight subjects for all cohorts). In order to enhance safety, the SRT may adjust dose-escalation cohort dose level for higher dose-escalation cohorts prior to subject enrollment to said cohort and after review of safety data from the study to date.

Table 3. Dose Cohorts

Dose Cohort	Number of KITE-222 CAR T Cells[a,b]	
	Subject Weight < 50 kg	Subject Weight ≥ 50 kg
Dose-escalation Cohort 1	CCI	
Dose-escalation Cohort 2		
Dose-escalation Cohort 3		
Expansion Cohort	The optimal dose for the expansion cohort will be determined by the SRT after completion of dose-escalation part	

Abbreviations: CAR, chimeric antigen receptor; SRT, safety review team.

a CCI

b A subject may receive the highest dose manufactured if it is less than the targeted dose after discussion with the Kite medical monitor. Out-of-specification product may be administered in line with the local regulation both during dose escalation and expansion phase.

The starting dose of KITE-222 CCI has been selected based on previous CAR T-cell therapy experience described in Section 1.4.3. It is anticipated that KITE-222 will have a safety profile comparable to that of other clinically tested CAR therapies such as anti-CD19 CAR T cells and anti-BCMA CAR T cells, except for an increased potential risk of prolonged neutrophil recovery compared with lymphodepleting chemotherapy or alternate CAR T-cell therapies.

Dose-escalation steps are no greater than half-log increases, based on the experience of other CAR T-cell product trials. A flat dose will be used for all subjects, as seen in anti-BCMA CAR T-cell trials and early anti-CD123 CAR trials; however, subjects weighing less than 50 kg will have a dose reduction of CCI to normalize dosing in the event of high subject variability from the expected mean weight (80 to 85 kg).

Additional doses beyond the current schema may be explored at the discretion of the SRT as described in Section 3.2.

For any enrolled subject whose manufacturing cannot reach the target dose level, the subject may receive the highest manufactured dose after discussion with the Kite medical monitor.

3.3.5. Conditioning Chemotherapy and Allo-SCT

Subjects treated with KITE-222 may initiate conditioning chemotherapy for allo-SCT only after disease assessment at Day 28. The decision to proceed to allo-SCT rests with the investigator, except if the patient is leukemia-free and has an ongoing KITE-222-related Grade 4 neutropenia by Day 28. The decision to start the conditioning chemotherapy should be discussed with the Kite medical monitor. Allo-SCT may also be used to consolidate response in subjects treated with KITE-222. Allo-SCT should be performed according to the treating institutions standard for the donor source, subject eligibility, conditioning chemotherapy regimen, cell dose, and management after allo-SCT.

3.4. Duration of Treatment and Study

3.4.1. Duration of Treatment

KITE-222 is a single dose treatment for subjects with r/r AML. After treatment, the subject will be monitored as an inpatient for a recommended 28 days (minimum of 14 days), unless discussed with the Kite medical monitor (additional information is in Section 3.2).

3.4.2. Duration of Subject Participation

The study consists of the screening period, enrollment, lymphodepleting chemotherapy, KITE-222 infusion, post-treatment follow-up after the infusion, and a follow-up period prior to transition onto a separate Kite Long-term Follow-up (LTFU) study (discussed in Section 3.5). The duration of the study for individual subjects will vary depending on a subject's response to treatment, survival, and timing of the transition onto the LTFU study.

For a subject who completes participation in this study and also completes the LTFU period in the separate LTFU study, the entire duration of a subject's participation in both studies will be up to approximately 15 years from the time of the initial infusion of KITE-222. The need for prolonged follow-up is based CCI [redacted] the need to understand and mitigate the potential risks of delayed onset AEs that could be the potential consequence of this emerging technology.

For patients who are enrolled but not dosed, the end of the study will be 30 days after the last procedure has been completed.

3.4.3. End of Study Definition

The end-of-study is defined as when the last remaining subject completes their last visit on this study and transitions to a separate LTFU study (Section 3.5), or when the last remaining subject, while still a participant in this study, is considered lost to follow-up, withdraws full consent, or dies.

3.5. Long-term Follow-up Study

After completing at least 24 months of assessments in this study, all subjects who received an infusion of KITE-222 will be transitioned to a separate LTFU study after providing informed consent, where they will be monitored for occurrence of late-onset targeted AEs/serious AEs (SAEs) including secondary malignancies and the presence of CCI [redacted] suspected to be related to KITE-222 through 15 years from the time of the initial KITE-222 infusion (refer also to Section 7.9). In the LTFU study, subjects will continue assessments at timepoints contiguous with their timepoints in this study.

3.6. Study Discontinuation Criteria

The SRT can make a recommendation to the sponsor to discontinue the study early based on the guidelines in the SRT charter. Refer to Section 8.9 for more information.

3.7. Number of Participating Sites

Approximately 15 study sites located in the US and European Union (EU) will participate in this study. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

3.8. Source Data

The source data for this study will be obtained from original documents/records, central laboratory, local laboratory, specialty laboratory (for pharmacokinetics and/or pharmacodynamics data), and/or electronic data capture (EDC).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

It is anticipated that approximately 40 subjects will be treated in this study as defined below:

- Dose-escalation Cohort: approximately 18 subjects, with the intent of identifying the MTD
- Expansion Cohort: approximately 22 subjects, with the intent to treat a minimum of 28 subjects across Phase 1 at the MTD

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

To be enrolled in the study, subjects must meet all of the following criteria:

1) R/R de novo or secondary AML as defined by the ELN 2017 Classification {Dohner 2017}, excluding acute promyelocytic leukemia (see specific requirements for France in Section 12.4):

    a) Refractory disease is defined as one of the following:

        i) Failed at least 2 cycles of a 7 + 3-based induction regimen, which may have been given in combination with a targeted agent, an antibody-based therapy, or a B-cell lymphoma (BCL)-2 inhibitor. For other agents added to the 7 + 3-based induction regimen, please discuss with the Kite medical monitor.

        ii) Failed at least 1 cycle of a purine analogue-based induction therapy, such as fludarabine or cladribine paired with anthracyclines and cytarabine (eg, FLAG-Ida, cladribine, ara-C, granulocyte colony-stimulating factor, and mitoxantrone [CLAG-M])

        iii) Failed any intensive re-induction regimen after at least 1 prior cycle of induction chemotherapy

        iv) Persistent AML after 4 cycles of therapy with an HMA (eg, decitabine or azacitidine)

        v) Persistent AML after 2 cycles of low-intensity venetoclax-based combinations such as venetoclax + HMA or venetoclax + LDAC

        vi) Failed therapy after remission (eg, consolidation) during any number of cycles (maximum of 4) of high- or intermediate-dose cytarabine

    b) Relapsed disease is defined as one of the following:

        i) First relapse, if RFS was less than 12 months following achievement of CR

ii) Relapsed disease after 2 or more lines of systemic therapy

iii) r/r disease after allo-SCT provided subject is at least 100 days from SCT at the time of enrollment and withdrawn from immunosuppressive medications for at least 4 weeks prior to enrollment

2) Aged 18 years or older

3) Morphological disease in the BM (≥ 5% blasts) and/or peripheral blood within 28 days before enrollment and no subsequent anti-AML therapy (except for hydroxyurea given for cytoreduction purposes). All subjects will require BM evaluation between screening and enrollment.

4) Prior exposure to the relevant agent class for subjects with AML characterized by a mutation targeted by an approved therapy (eg, FLT3- internal tandem duplication [ITD], isocitrate dehydrogenase [IDH]1, or IDH2).

5) Institutional criteria for allo-SCT fitness must be met: subjects must have an identified stem-cell donor readily available for potential allo-SCT after therapy with KITE-222. The donor may be matched or mismatched, cord, haplo-identical, or other and declared suitable according to the treating institution's standard criteria.

6) Prior medications:

a) At the time the subject is planned for leukapheresis, at least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic or targeted agents (eg, chemotherapy, HMA, BCL-2 inhibitor, IDH inhibitors, FLT3-ITD inhibitors, antibody-drug conjugates, or monoclonal antibodies).

b) At the time the subject is planned for leukapheresis, at least 6 months must have elapsed since treatment with alemtuzumab and at least 3 months must have elapsed since treatment with clofarabine, fludarabine, or cladribine.

c) At the time the subject is planned for leukapheresis, at least 3 half-lives must have elapsed since any prior systemic inhibitory or stimulatory immune checkpoint molecule therapy (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, or T-cell engagers).

d) Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids; any physiologic steroid replacement is an exception) and other immunosuppressive drugs must be avoided for 7 days before enrollment

e) Toxicities due to prior therapy must be stable and have recovered to Grade 1 or lower (except for clinically nonsignificant toxicities such as alopecia)

7) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

8) Adequate hematologic status, defined as:

   a) Absolute neutrophil count (ANC) ≥ 1000/μL unless, in the opinion of the investigator, cytopenia is due to underlying leukemia

   b) Platelet count ≥ 50,000/μL unless, in the opinion of the investigator, thrombocytopenia is due to underlying leukemia

   c) Absolute lymphocyte count (ALC) ≥ 100/μL

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

   a) Creatinine clearance (as estimated by the Cockcroft-Gault formula) ≥ 60 mL/min

   b) Serum alanine aminotransferase/aspartate aminotransferase ≤ 2.5 × upper limit of normal

   c) Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's syndrome

   d) Cardiac ejection fraction ≥ 50%, no clinically significant pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings

   e) Baseline oxygen saturation > 92% on room air and no clinically significant pleural effusion as determined by chest imaging.

10) Contraception: male and female subjects of childbearing potential must agree to use an effective method of contraception for a minimum of 12 months after the study treatment

11) Pregnancy testing: 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 before enrollment are not considered to be of childbearing potential).

4.2.2. Exclusion Criteria

To be enrolled in the study, subjects must not meet any of the following criteria:

1) Diagnosis of acute promyelocytic leukemia

2) Auto-SCT within the 6 weeks before enrollment

3) DLI within 28 days prior to enrollment

4) Any drug used for graft-versus-host disease (GVHD) within 4 weeks prior to enrollment (eg, calcineurin inhibitors, methotrexate, mycophenolate, rapamycin, thalidomide, or JAK-2 inhibitors) or immunosuppressive antibody used within 4 weeks prior to enrollment (eg, anti-CD20, anti-tumor necrosis factor (anti-TNF), anti-IL 6, anti-IL 6 receptor, or anti-IL-2)

5) Acute GVHD grade II-IV by Mount Sinai Acute GVHD International Consortium criteria {Harris 2016}; acute or chronic GVHD requiring systemic treatment within 4 weeks prior to enrollment

6) Active central nervous system (CNS) disease involvement. If the subject has had prior history of CNS AML, they must have a negative cerebrospinal fluid (CSF) cytospin and magnetic resonance imaging (MRI) or computed tomography (CT) (if MRI is not feasible) of the brain demonstrating no evidence of CNS disease.

7) Requirement for urgent therapy due to ongoing or impending oncologic emergency (eg, leukostasis or tumor lysis syndrome [TLS]) or the possible requirement for urgent therapy due to ongoing or impending oncologic emergency (eg, spinal cord compression, bowel obstruction, leukostasis, or TLS) at the time of enrollment or KITE-222 infusion

8) History of CLL-1-directed therapy or genetically modified T-cell therapy

9) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, or breast) unless disease free for at least 3 years after the last definitive therapy

10) History of severe hypersensitivity reaction to aminoglycosides or any of the agents (including fludarabine and cyclophosphamide) used in this study

11) History of concomitant genetic syndrome associated with BM failure such as Fanconi anemia, Kostmann syndrome, or Shwachman-Diamond syndrome

12) Subjects with a genetic syndrome that increases the risk of allo-SCT, including Down syndrome (trisomy 21)

13) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, atrial fibrillation, or other clinically significant cardiac disease within 12 months before enrollment

14) Subjects with cardiac atrial or ventricular leukemia involvement

15) History of symptomatic deep vein thrombosis (DVT) or a pulmonary embolism within 6 months of enrollment. History of upper extremity line related DVT within the 3 months of conditioning chemotherapy.

16) Primary immunodeficiency disorders

17) History of a 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 the current Infectious Diseases Society of America or applicable country guidelines

18) History of an autoimmune disease (eg, Crohns disease, rheumatoid arthritis, or systemic lupus) resulting in end-organ injury or requiring systemic immunosuppression or systemic disease modifying agents within the last 2 years. Subjects with a history of autoimmune-related thyroiditis on a stable dose of thyroid replacement hormone and subjects with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

19) History or presence of cerebrovascular ischemia, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement. History of seizures is acceptable if there are no episodes in the last 5 years. History of bleeding in the CNS is acceptable if related to thrombocytopenia of the AML, more than 12 months have elapsed, and there is complete resolution of symptoms and cerebral imaging.

20) Presence or suspicion of a fungal, bacterial, viral, or other infection that is uncontrolled or requiring antimicrobials for management. Prophylactic antimicrobial therapy is acceptable. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if they are responding to active treatment and after consultation with the Kite medical monitor.

21) Live vaccine received within the ≤ 4 weeks before enrollment, or anticipation of the need for a live vaccination during the course of the study

22) Inability to tolerate prophylactic antifungal and antibacterial therapy.

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

24) Ongoing Grade 2 or higher toxicities from previous therapies, excluding hematologic toxicities. Subjects with peripheral neuropathy of any grade or clinically nonsignificant toxicities (eg, alopecia) of any grade may be eligible.

25) Females of childbearing potential who are pregnant or breastfeeding (the required preparative chemotherapy may have dangerous effects 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.

26) Any medical or psychiatric condition likely to interfere with the assessment of safety or efficacy of the study treatment

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

4.3. 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 the study-required treatment and/or other protocol-required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent. The investigator is to discuss with the subject about the appropriate procedures for withdrawal from the study (refer to Section 7.13).

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol-required therapy or undergo procedures and the subject does not wish to continue further study follow-up. The investigator is to discuss with the subject about the appropriate procedures for withdrawal from the study (refer to Section 7.13).

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

4.3.1. Reasons for Removal From Treatment

Reasons for removal of a subject from protocol-required Ips or procedures include any of the following:

- AE
- Withdrawal by the subject
- Product not available
- Subject is lost to follow-up
- Subjects dies
- Termination of the study by the sponsor
- Other (eg, investigator decision or noncompliance)

4.3.2. Reasons for Removal From Study

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

- Withdrawal by the subject
- Subject is lost to follow-up
- Subject dies
- Termination of the study by the sponsor
- Other (eg, investigator decision or noncompliance)

4.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified number of subjects are attained in the DLT-evaluable and modified intent-to-treat (mITT) analysis sets. Subjects who discontinue the study before the end of the study will not be replaced. Refer to Section 9.7.1 for the definition of the DLT-evaluable and mITT analysis sets.

4.5. Pregnancy and Lactation

There is no relevant clinical experience with KITE-222 in pregnant or lactating women, and animal reproductive studies have not been performed. This experimental therapy should not be administered to pregnant females or females who are breastfeeding. Females of childbearing potential must have a negative pregnancy test before enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Females of childbearing potential should be monitored according to the local and country-specific regulations. Refer to Section 12.3 for the definition of childbearing potential.

Female subjects and female partners of male subjects are recommended to use a highly effective contraception (the method must achieve an annual failure rate of < 1%) through at least 12 months after the lymphodepleting chemotherapy dosing or the administration of KITE-222, whichever is longer. Male subjects are recommended to not father a child for at least 12 months after completing the lymphodepleting chemotherapy dosing or administration of KITE-222, whichever is longer. Refer to Section 12.3 for a complete list of highly effective contraception methods.

Refer to Section 8.8.2.1 for reporting instructions for any pregnancy or lactation cases.

Refer to Table 10 footnote Q for recommended pregnancy testing during the trial.

5. INVESTIGATIONAL PRODUCT

5.1. Randomization, Blinding, and Treatment Codes

Not applicable.

5.2. Description of Investigational Product

KITE-222 is an autologous CAR T-cell therapy that is manufactured from a subject's own T cells. The subject's T cells are collected by leukapheresis and genetically engineered ex vivo to express a CAR specific for the CLL-1 target antigen.

Each subject's leukapheresed cells are shipped to the CPF, where they are processed [redacted]. Selected cells are then activated and transduced with a [redacted] vector to introduce the anti-CLL-1 CAR gene. The engineered T cells are then further expanded and cryopreserved to generate the IP (KITE-222) per CPF standard operating procedures.

After manufacture and passing the release criteria, KITE-222 will be delivered to the clinical site frozen in cryostorage bags in a liquid nitrogen dry shipper, as described in the Investigational Product Manual (IPM). The bags must be stored in vapor phase of liquid nitrogen and the product must remain frozen until the subject is ready for the treatment. Upon receipt of KITE-222 at the treatment facility, verification that the product and subject-specific labels match the subject's information (subject identification [ID] number) is essential.

Refer to the IPM for details about shipping of the leukapheresis material to the CPF, manufacture of KITE-222, and delivery of the product to the clinical site.

In exceptional cases, a KITE-222 product lot that does not meet certain release specification criteria may be administered to a subject, when necessary to avoid an immediate significant hazard to the subject and having considered alternative options including the product lot remanufacture. Relevant country regulations will be followed and notifications to concerned regulatory agencies and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be performed as necessary per local requirements, in case such out-of-specification product lot is supplied and administered to a subject.

5.3. Packaging, Labeling, Storage, and Handling of Investigational Product

Refer to the IPM for details about the KITE-222 formulation, packaging and labeling, instructions for storage and handling, and ordering of clinical supplies.

5.4. Dosage and Administration

Refer to Section 3.3.4 for KITE-222 planned dose levels. Refer to Section 7.7.3 for list of the assessments and procedures to be performed on the day of KITE-222 administration. Refer to the IPM for details and instruction on administration of KITE-222.

Administration or dosing errors (eg, whether the complete volume in the bag was administered to the subject) should be documented in the subject's source documentation and respective electronic case report form (eCRF).

5.5. Prior and Concomitant Medications

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care to the subject except those medications listed in Section 5.6. Prior medications contained in the excluded medications list should be discussed with the Kite medical monitor. Refer to current IB for more information about supportive therapy, and to Section 6.3.12 for information about recording prior and concomitant medications.

5.6. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids; any physiologic steroid replacement is an exception) and other immunosuppressive drugs must be avoided for the 7 days before leukapheresis and 5 days before KITE-222 administration but may be continued if required as a replacement therapy.

Systemic corticosteroids must also be avoided as a premedication in subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance) if the administration is within the 7 days before leukapheresis or 5 days before KITE-222 administration. Such subjects should instead undergo MRI scans with contrast or CT scans without contrast during the washout period specified above. In such cases, alternative or alternative dyes such as gadolinium may be considered at the investigator's discretion.

Corticosteroids and other immunosuppressive drugs (with the exception of physiologic steroid replacement) should also be avoided for 3 months after KITE-222 administration, unless they are used to manage KITE-222-related toxicities, are used as conditioning for allo-SCT, or their use is discussed with the Kite medical monitor. Other medications that might interfere with the evaluation of KITE-222, 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 whenever possible for subjects who are at risk of bleeding due to thrombocytopenia. If a subject requires initiation of the therapeutic anticoagulant doses before initiation of the lymphodepleting chemotherapy or before KITE-222 infusion, the lymphodepleting chemotherapy or KITE-222 infusion must be held and the case discussed with the Kite medical monitor.

Treatment for a subject's leukemia, such as chemotherapy, immunotherapy, targeted agents, radiation, high-dose corticosteroids (other than those defined or allowed in this protocol or as part of the conditioning chemotherapy before the allo-SCT), and other investigational agents are prohibited, except as needed for the treatment of disease progression or relapse after KITE-222 infusion.

Medications with sedative properties should be avoided if possible in the setting of neurologic events (refer to current IB). If permissibility of a specific medication or treatment is in question, please contact the Kite medical monitor.

5.7. Accountability and Return of Investigational Product

Refer to the KITE-222 IPM for details about accountability of KITE-222.

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The study monitor will review study drug records at periodic intervals.

6. STUDY ASSESSMENTS

Study assessments described in this section are to be performed according to the schedule presented in the SOA (Table 10, Table 11 [follow-up without allo-SCT], and Table 12 [follow-up after allo-SCT]) in Section 12.2.

6.1. Demographic Data

Demographic data will be collected at screening for each subject as per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity, and country of enrollment with the intent to assess the possible association of demographics with subject safety and treatment effectiveness.

6.2. Medical and Treatment History

Relevant medical history before the start of AE reporting (ie, from before enrollment [leukapheresis]) will be collected. Relevant medical history is defined as data about the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the eCRFs.

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. Copies from the subjects' chart should be obtained for subjects who are being referred from another clinic or institution to the participating study sites.

6.3. Safety Assessments

Safety assessments will include collection of AEs, clinical laboratory tests, physical examination, weight, vital signs, neurologic examinations, ECOG performance status, cardiac function, brain MRI or CT (if MRI is not feasible), lumbar puncture, collection of concomitant medications, and assessment of the presence of anti-KITE-222 antibodies CCI , as described in the following sections.

Safety assessments will be conducted according to the schedule presented in the SOA (Table 10, Table 11, and Table 12).

6.3.1. AEs

All AEs, SAEs, and DLTs will be collected at each study visit as indicated in the SOA (Table 10, Table 11, and Table 12). Subjects will be asked about any AEs that might have occurred since the last study visit.

6.3.2. Clinical Laboratory Tests

Blood, serum, or urine samples will be collected for clinical laboratory tests at the time points indicated in the SOA (Table 10, Table 11, and Table 12). Additional samples may be collected as

needed for further safety testing if clinically indicated. Except for assays for anti-KITE-222 CAR antibodies CCI (performed at the central laboratory), all clinical laboratory test assessments listed in Table 4 will be performed at the local laboratory.

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Table 4. Clinical Laboratory Tests for Safety Assessments

Serum Chemistries (Serum)	Hematology (Blood)	Other (Serum)	Other (Plasma)
Albumin	CBC with differential[b]	Pregnancy test[d]	Coagulation[g]
ALT	Absolute lymphocyte count	CRP[e]	
ALP		Ferritin[f]	
AST	**PBMCs:**	Serologic testing[f]	
Bicarbonate (CO_2) total (as clinically indicated)	CCI	Anti-KITE-222 CAR antibodies (central laboratory)	
Bilirubin total and direct			
BUN or urea[a]			
Calcium total			
Chloride			
Creatinine			
Creatinine clearance (as estimated by Cockcroft-Gault formula) (screening and prior to lymphodepleting chemotherapy only)			
Glucose			
Inorganic phosphorus			
Lactic acid (as clinically indicated)			
LDH			
Magnesium total			
Potassium			
Sodium			
Uric acid			

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CAR, chimeric antigen receptor; CBC, complete blood count; CRP, C-reactive protein; EU, European Union; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; PBMC, peripheral blood mononuclear cell; CCI .

Notes: Laboratory tests listed above are performed at the local laboratory, except for anti-KITE-222 CAR antibodies, CCI and unless otherwise indicated.

a. If BUN test cannot be analyzed by the local laboratory, urea should be analyzed.
b. Per institutional guidelines, but must include white blood cell count, neutrophils or absolute neutrophil count, lymphocytes or absolute lymphocyte count, hemoglobin, platelets, and quantification of the percentage of blasts.
c. Refer to Section 6.7 for information on CCI testing.
d. A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test (beta-human chorionic gonadotropin [β-hCG]) is positive, the subject should not be enrolled. If a standard-of-care pregnancy test is collected during the course of the study, and the result is positive, the investigator should report the

pregnancy to Kite per instructions specified in Section 8.8.2.1. If a female partner of a male subject becomes pregnant during the conduct of the study, the pregnancy must be reported to Kite per instructions specified in Section 8.8.2.1.

e. CRP and ferritin will also be tested at the central laboratory as part of the pharmacodynamics evaluation (ie, key analytes including cytokines; refer to Section 6.6) at the time points listed in the schedule of assessments (Table 10, Table 11, and Table 12).
f. At EU sites, serologic tests (ie, HIV, hepatitis B virus, hepatitis C virus, and syphilis) will be carried out per institutional guidelines and EU regulations. This may be done within 30 days before leukapheresis and/or on the day of leukapheresis.
g. Coagulation must include prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen at the time points listed in the schedule of assessments (Table 10).

6.3.3. Physical Examination

Physical examinations will be performed during screening and at times noted in the SOA (Table 10, Table 11, and Table 12). At subsequent examinations, clinically significant adverse changes (as determined by the investigator) when compared with the baseline exam will be reported as AEs.

6.3.4. Weight

Weight (and height) will be collected during screening and at times noted in the SOA (Table 10), and as per local standard of care.

6.3.5. Vital Signs

Vital signs include blood pressure, heart rate, respiration rate, oxygen saturation, and temperature. Vital signs will be monitored as indicated in the SOA (Table 10, Table 11, and Table 12).

During KITE-222 administration, vital signs will be monitored before and after the KITE-222 infusion and then routinely per institutional guidelines. Vital signs may be monitored more frequently as clinically indicated.

6.3.6. Cardiac Function

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

If the last chemotherapy regimen the subject received is not considered cardiotoxic, then an ECHO performed within the 28 days before signing the informed consent may be used for eligibility. If the last chemotherapy regimen the subject received is considered cardiotoxic, then an ECHO performed at least 14 days after the subject received their last chemotherapy treatment and within the 28 days before signing the consent may be used for confirmation of eligibility.

To establish a baseline, an ECG will be performed during the screening period. ECG assessments will include PR interval, QRS interval, QT interval with corrected QT (QTc), and RR interval. QTc interval will be calculated using Fridericia's formula (QTcF) {Fridericia 2003}.

6.3.7. Chest Imaging

As indicated in the SOA (Table 10), each subject must have screening chest imaging performed within 7 days before enrollment to confirm eligibility. Either a chest x-ray or CT or MRI scan of the chest with or without contrast can be used to demonstrate no significant pulmonary pathology. Refer to Section 12.4 for country-specific requirements.

6.3.8. Neurologic Examinations and Assessments

The subject's neurological status will be evaluated at screening to establish a baseline. After enrollment/leukapheresis, subjects will be evaluated for any neurological symptoms at each of the time points specified in the SOA (Table 10). During the hospitalization period for subjects treated with KITE-222, evaluations of neurological status may need to be increased. Changes in neurological status should be reported as an AE if considered clinically significant at the discretion of the investigator.

Neurological assessments will be standardized by using the immune-effector cell-associated encephalopathy (ICE) score (Section 12.6) {Lee 2019}. The ICE is a 10-point, 5-question evaluation that covers orientation, naming, following commands, writing, and attention.

In subjects who developed Grade 2 or higher immune-effector cell-associated neurotoxicity syndrome (ICANS), ICE score should be determined daily until resolution of ICANS and return to baseline neurological status.

6.3.9. ECOG

Subject's performance status as measured by the ECOG scale will be performed at time points specified in the SOA (Table 10) to quantify the subject's general well-being and ability to perform activities of daily life.

6.3.10. Brain Magnetic Resonance Imaging

Subjects with a prior history of CNS involvement by AML or clinical symptoms suggestive of neurological involvement will undergo a brain MRI or CT (if MRI is not feasible) during the screening period to rule out CNS disease and to establish a baseline. The MRI scan will be performed with contrast wherever possible or without contrast in case of contraindication. An MRI performed after the subject's last chemotherapy treatment and ≤ 28 days before signing the informed consent may be used for confirmation of eligibility.

Refer to the current IB for radiological examination to be performed as part of the evaluation of any new onset of neurologic toxicities of severity Grade 2 or higher.

6.3.11. Lumbar Puncture

Lumbar puncture will be performed at the time points specified in the SOA (Table 10). Opening pressures should be measured with each lumbar puncture when possible and recorded in the subject's site chart.

- Screening: Subjects with a history of CNS malignancy, leptomeningeal carcinomatosis, symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical examination, will undergo lumbar puncture at the screening visit for examination of CSF to determine the presence of CNS malignancy.

- After infusion: A lumbar puncture is recommended for subjects with new onset of clinically significant neurologic toxicities of severity Grade 2 or higher after KITE-222 infusion unless contraindicated. CSF samples obtained after the infusion will be submitted to the central laboratory and analyzed for levels of key analytes (including cytokines) and the presence of CAR T cells.

6.3.12. Concomitant Medications

Information about concomitant medications will be collected at time points specified in the SOA (Table 10, Table 11, and Table 12). Reporting requirements for concomitant medications are provided in Table 5. Specific concomitant medication collection requirements and instructions are included in the eCRF completion guidelines. Refer to Sections 5.5 and 5.6 for information about allowed/excluded medications.

Table 5. Reporting Requirements for Concomitant Medications

Not Enrolled (ie, Screen Fails, or Not Leukapheresed)	Enrolled (Leukapheresed), But Do Not Receive KITE-222	Enrolled (Leukapheresed), And Receive KITE-222
Concomitant therapies related to SAEs will be recorded from the date of the screening informed consent through 30 days after the last study-specific screening procedure.	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, lymphodepleting chemotherapy) or until the initiation of a new anticancer therapy, whichever occurs first.	• Concomitant therapies[a] including medications, oxygen, and blood products will be recorded from the date of the informed consent until 3 months after completing treatment with KITE-222. • After the 3-month follow-up period or after the start of the conditioning regimen for allo-SCT, whichever occurs first, only targeted concomitant therapies will be recorded until either 24 months after KITE-222 infusion or until disease progression or relapse, whichever occurs first. If a targeted AE/SAE occurs after the concomitant medication follow-up period, all relevant concomitant medications administered for the treatment of the targeted AE/SAE shall also be recorded. — Targeted concomitant therapies include immunosuppressive drugs, anti-infective drugs, marrow growth factors, tyrosine kinase inhibitors, and vaccinations.

Abbreviations: AE, adverse event; allo-SCT, allogeneic hematopoietic stem-cell transplantation; SAE, serious adverse event.
Concomitant procedures of intubation and dialysis will follow the same reporting requirements as for concomitant therapies.

6.3.13. Other Safety Assessments

6.3.13.1. Anti-KITE-222 Antibodies

The presence of anti-KITE-222 antibodies in the subject's serum will be monitored at time points identified in the SOA (Table 10, Table 11, and Table 12).

6.3.13.2. CCI

As KITE-222 comprises CCI vector-transduced T cells, the presence of CCI in the blood of treated subjects will be monitored. PBMCs for CCI testing will be obtained at baseline (before leukapheresis), and at Month 3, Month 6, and Month 12. Samples will be held for up to 15 years. Only if a subject's PBMC sample tests positive for CCI at any time point within the first year, samples will continue to be collected and tested annually for up to 15 years or as clinically indicated (ie, if any clinical reason to suspect CCI).

6.3.13.3. Assessments in the Event of a Secondary Malignancy

Secondary malignancies are defined as the development of any new malignancies, with the exception of a relapse of the primary malignancy, occurring after the administration of KITE-222.

In the case of a secondary malignancy, every effort will be made to obtain a blood sample (PBMC) and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to start a testing workflow, including tests such as transgene elements, CCI presence of common cancer-drivers/mutations and insertional mutagenesis. Please refer to Section 12.4 for additional country-specific requirements.

6.4. Disease Assessments

Disease assessments will be performed according to the schedule presented in the SOA (Table 10, Table 11, and Table 12). Subjects with symptoms suggestive of disease progression or relapse should be evaluated for progression at the time symptoms occur even if this requires an unscheduled visit.

Subjects will be evaluated for disease assessment by the site investigator at times indicated in the SOA. Whether or not subjects are in morphologic remission (BM blasts are < 5%), samples should be sent to the central laboratory for potential evaluation of MRD (eg, MFC for MRD and quantitative polymerase chain reaction [qPCR] for nucleophosmin [NPM]1 mutations in applicable subjects). The percentage of locally evaluated BM blasts should be entered in the eCRF. In addition, local CBC with differential, including the percentage of blasts, should be assessed within 3 days of any marrow sampling, although the date of marrow sampling is assigned as the date of disease assessment.

In subjects with prior extramedullary disease, disease assessment requires imaging evaluation of extra medullary disease to confirm remission and should be entered into the eCRF.

After Day 28, no subsequent disease assessments are needed if progression or relapse has already been shown in the previous assessment.

6.4.1. Bone Marrow Evaluation and Disease Assessment

BM aspirates and biopsies will be collected throughout the study per the SOA (Table 10, Table 11, and Table 12) and/or standard of care. BM aspirate and biopsy samples will be processed and submitted to the central laboratory as outlined in the central laboratory manual. Refer to the laboratory manual for collection, processing, and shipment requirements; note that some samples (eg, BM sample for MRD and CLL-1 expression) must be shipped on the same day of collection. An overview of the sample types that will be required is provided below.

To confirm a CR, CRMRD$^-$, Cri, or MLFS, the BM must show no evidence of disease by morphology. Disease assessments will be evaluated per the ELN 2017 Classification {Dohner 2017} (Section 12.5).

CCI [redacted]

Screening BM evaluations will include the following:

- Archival formalin-fixed paraffin-embedded (FFPE) BM block and/or unstained slides used for the original diagnosis of AML (if available), to be submitted to the central laboratory along with the pathology report.
- BM aspirate and biopsy samples, to be collected after the last dose of systemic chemotherapy and within approximately 14 days before enrollment.
  - If a fresh BM aspirate and biopsy was recently performed and collected samples were properly stored before consent was given, the Kite medical monitor should be consulted to confirm the sample is acceptable for screening and central laboratory purposes.
- In subjects who receive bridging therapy, an additional BM sample must be acquired to ensure morphologic disease, regardless of whether there is evidence of disease by circulating peripheral blasts. This assessment should occur between the end of bridging therapy and Day −5.

On-study BM evaluations will include the following:

- BM aspirates and biopsy samples for subjects who do not proceed to allo-SCT, as per the SOA (Table 10 and Table 11) and in those who do proceed to allo-SCT, as per the SOA (Table 10 and Table 12).
  - No more than 1 BM evaluation would be required per week in the event of an unscheduled BM evaluation or planned initiation of allo-SCT conditioning chemotherapy.
  - If a subject has a BM evaluation earlier than the indicated per-protocol time point, then the BM samples should be processed and submitted to the central laboratory per the central laboratory manual.
  - For subjects who undergo an allo-SCT, BM evaluations for response assessment are required 30 days after allo-SCT.
  - CCI [redacted]
- BM biopsies will be performed as per the SOA (Table 10, Table 11, and Table 12) and at any time when the BM aspirate is either a dry tap or hemodiluted, the BM biopsy will be used to determine disease burden by immunohistochemistry analyses. Refer to Section 12.4 for country-specific requirements.
- Fresh BM aspirates are submitted to the central laboratory as outlined in the central laboratory manual.
- BM biopsies are submitted to the central laboratory as outlined in the central laboratory manual.

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

BM aspirate/biopsy should also be considered to evaluate hemophagocytic lymphohistiocytosis (HLH) as indicated in the IB. A portion of the BM sample collected to evaluate HLH or other toxicities should be submitted to the central laboratory as outlined in the central laboratory manual.

6.4.2. Measurable Residual Disease

Whether or not subjects are in morphologic remission (BM blasts are < 5%) additional studies will be performed via central laboratory for potential evaluation of MRD.

Monitoring of MRD to determine the presence of residual leukemic blasts will be performed by MFC on BM aspirates. CCI [redacted]

In addition, in subjects with a known NPM1 mutation, detection of mutated NPM1 in peripheral blood is a well-validated method to detect MRD {Ivey 2016}. Disease assessments for both subjects who do and do not undergo allo-SCT will include peripheral blood NPM1 analysis if applicable based on disease history. Samples should be submitted to the central laboratory at disease assessment time points as noted in the SOA (Table 10, Table 11, and Table 12) as part of the blood draws for CLL-1 expression.

CCI [redacted]

CCI [redacted]

[redacted]

6.4.4. Imaging Requirements (for Subjects with Known Non-CNS Extramedullary Disease at Baseline)

Extramedullary disease will be assessed at screening with an imaging modality appropriate for the anatomical site and clinical scenario. For all subjects with known non-CNS extramedullary disease, images must be taken within 28 days before enrollment and after the last anticancer therapy. In addition, for subjects receiving bridging therapy, images must be repeated after bridging therapy has completed.

After KITE-222 infusion, repeat imaging with disease assessments is required from Week 4 through Month 24 or relapse (Table 10, Table 11, and Table 12), whichever occurs first. In subjects who achieve CR, CRMRD$^-$, or CRi, imaging may be stopped until evidence of disease relapse.

All on-study assessments of extramedullary disease detected through imaging should be made with the same imaging modality and of the same anatomical locations as imaged at baseline.

For all subjects, extramedullary disease imaging assessments should be performed per standard of care anytime the subject presents with symptoms suggestive of disease progression or relapse, as per the SOA (Table 10, Table 11, and Table 12).

6.5. Pharmacokinetic Assessments

PBMC samples for pharmacokinetic assessments will be drawn according to the schedule presented in the SOA (Table 10, Table 11, and Table 12).

Pharmacokinetic assessments include monitoring of the presence, expansion, persistence, and immunophenotype of transduced anti-CLL-1 CAR T cells in the blood over time, primarily by polymerase chain reaction (PCR) analysis and complemented by flow cytometry. Expansion and persistence in peripheral blood is monitored by a CLL-1 CAR-specific ddPCR assay.

6.6. Pharmacodynamic Assessments

Serum samples for pharmacodynamic assessments will be drawn according to the schedule presented in the SOA (Table 10, Table 11, and Table 12).

Pharmacodynamic assessments of KITE-222 will include monitoring levels of key analytes in the serum over time. CCI

Biomarker analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for KITE-222. Prognostic markers specific for AML and related to the tumor immune environment may also be evaluated in archived and fresh extramedullary tumor biopsies.

CSF, as well as additional samples , may be harvested from subjects who develop ICANS or CRS to enable the evaluation of inflammatory cytokines and chemokine levels. As applicable, lymphocyte or myeloid populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of KITE-222.

CCI

CCI [redacted]

[redacted]

[redacted]

7. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are described below and will be performed at the time points presented in the SOA (Table 10, Table 11, and Table 12) in Section 12.2.

The investigator must document any deviation from the protocol procedures and notify Kite or contract research organization (CRO).

7.1. Subject Informed Consent

Before a prospective subject can participate in the clinical study, the investigator must obtain written informed consent from the subject after adequate explanation of the study design, the anticipated benefits, and the potential risks. Subjects should sign the most current IRB/IEC-approved ICF before any study-specific activity or procedure is performed. Refer to Section 10.1.3 for more information about the informed consent process.

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

7.2. Subject ID Assignment

Each subject who enters the screening period will receive a unique subject ID number before any study-specific procedure or activity is initiated. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. Furthermore, the subject ID number must remain constant throughout the entire clinical study and must not be changed after enrollment or if the subject is rescreened or enrolled in a LTFU study.

7.3. Screening Period

The 14-day screening period begins on the date the subject signs the IRB/IEC-approved ICF and continues through the confirmation of enrollment (ie, commencement of leukapheresis [Section 7.6.1]) or until the subject withdraws consent before enrollment or it is determined that the subject is a screen failure (ie, does not meet the eligibility criteria per Section 4.2). Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, the date the subject was enrolled, or the reason for why the subject failed the screening. These data will be entered in the eCRF.

Informed consent must be obtained before completion of any nonstandard of care study-specific procedures. Procedures that are part of the standard of care are not considered study-specific procedures and may be performed before obtaining consent and used to confirm study eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA (Table 10).

After written informed consent has been obtained, the subject will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 4.2 and who commence leukapheresis will be enrolled in the study. If at any time before enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log and the reasons for failing screening should be documented.

The following assessments/procedures are to be completed during the screening period at the time points indicated in the SOA (Table 10):

- Demographic data
- Medical history and disease assessments
- Identification of donor source and assessment of fitness for allo-SCT per institutional standard
- Previous cancer treatment history
- Physical examination including height and weight
- Vital signs
- ECOG performance status
- Neurologic examination and assessment
- ECHO for left ventricular ejection fraction and pericardial effusion assessment
- ECG
- Brain MRI or CT (if MRI is not feasible) if there is a prior history of CNS involvement by AML or if clinical symptoms are suggestive of neurological involvement
- Chest imaging: x-ray or CT or MRI scan. Refer to Section 12.4 for country-specific requirements.
- Lumbar puncture for collection of CSF for determination of the presence of CNS malignancy, as indicated by a history of CNS malignancy, history of leptomeningeal carcinomatosis, or presence of clinical signs and symptoms of CNS malignancy
- Local laboratory assessments
  - Chemistry panel (including creatinine clearance, as estimated by the Cockcroft-Gault formula) (serum)
  - Coagulation (plasma)

- CBC with differential and percentage of blasts (blood)
- Beta-human chorionic gonadotropin (β-hCG) pregnancy test (serum or urine) on all females of childbearing potential
- For EU sites, serologic tests (ie, HIV, hepatitis B virus, hepatitis C virus, and syphilis) will be carried out per institutional guidelines and EU regulations. This may be done within 30 days before leukapheresis and/or on the day of leukapheresis. Refer to Section 12.4 for additional country-specific requirements.

- Screening BM evaluation
  - If there is > 4 week delay between screening BM sample collection and the planned administration of KITE-222, the Kite medical monitor should be consulted for guidance on whether the BM evaluation needs to be repeated prior to lymphodepleting chemotherapy.
  - If a fresh BM aspirate and biopsy was recently performed and collected samples were properly stored before consent was given, the Kite medical monitor should be consulted to confirm the sample is acceptable for screening and central laboratory purposes.
  - If available, an archival FFPE BM block and/or slides used for the original diagnosis of AML will be submitted to the central laboratory.
- Imaging studies as required for extramedullary disease (refer to Section 6.4.3)
- SAE reporting (refer to Section 8.5 for safety reporting guidelines)
- Concomitant medications documentation

7.3.1. Antiproliferative Treatment Administered During the Screening Period

CCI can be administered if a patient requires antiproliferative treatment during the screening period, provided the corresponding washing-out period before the planned apheresis is met (described in inclusion criterion 6). If it has been administered after the marrow assessment has been performed, a repeat assessment will be needed before the lymphodepleting regimen starts (see Section 7.6.2).

7.4. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the 14-day screening period will be permitted to rescreen once for an additional second 14-day screening period. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 14 days after signing of the original informed consent, the assessment or procedure that initially resulted in the subject failing screening will be performed, including any other procedures that fell outside of the designated screening window (eg, laboratory assessments and BM aspirate and biopsy); all other initial screening procedures/assessments do not need to be

repeated. If rescreening occurs, or leukapheresis is delayed for more than 28 days after the signing of the original informed consent, the subject must be reconsented and all screening procedures/assessments must be repeated.

7.5. Enrollment

A subject is considered to be enrolled in the study at the commencement of leukapheresis. Before commencement of leukapheresis, subjects must have undergone screening procedures and their results must have been confirmed to meet the study eligibility criteria (Section 4.2). If there is a need for a subject to have the leukapheresis repeated, then they must continue to meet the study eligibility criteria before the repeat leukapheresis procedure is performed.

7.6. Pretreatment Period

7.6.1. Leukapheresis/Enrollment

Leukapheresis/enrollment is to be performed approximately 7 days after eligibility confirmation. Refer to Section 3.3.1 for a description and definition of leukapheresis. Before leukapheresis commences, the following criteria must be met:

- In general, all eligibility criteria that were confirmed during screening must not be known to be violated before leukapheresis. Additionally, the investigator must review and confirm that the last CBC with differential and percentage of blasts and chemistry panel drawn before the start of leukapheresis must meet the eligibility criteria detailed in inclusion criteria 8) and 9) (Section 4.2.1). If any screening assessments or procedures are repeated between the confirmation of eligibility and the start of leukapheresis and results are outside of the eligibility criteria listed in Section 4.2.2, the subject should not be leukapheresed and the Kite medical monitor must be consulted.

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

- If leukapheresis is delayed for more than 7 days after eligibility confirmation, a CBC with differential and percentage of blasts and chemistry panel must be repeated.

- If the WBC count from a sample collected at the time of leukapheresis is CCI [redacted] the Kite medical monitor must be consulted before proceeding with leukapheresis.

- Corticosteroid therapy at a pharmacologic dose CCI [redacted] and other immunosuppressive drugs must be avoided for 7 days before leukapheresis (see Section 5.6).

In case of a manufacturing or leukapheresis failure, leukapheresis may be repeated.

See Section 5.6 for medications that are not allowed before leukapheresis occurs.

The following assessments/procedures are to be completed on the leukapheresis collection day (enrollment) and as outlined in the SOA (Table 10):

- Vital signs
- Weight
- Local laboratory assessments: Blood or serum samples for the following laboratory assessments must be drawn before leukapheresis either on the day of or the day before leukapheresis, unless otherwise noted:
  - Chemistry panel (serum)
  - Coagulation (plasma), includes prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen
  - CBC with differential and percentage of blasts (blood)
  - CRP, ferritin, and lactate dehydrogenase (LDH) (serum) (within 7 days before leukapheresis); if CRP is > 100 mg/L, the Kite medical monitor must be consulted before proceeding with the leukapheresis
  - Assay for donor chimerism (when available) for subjects with prior allo-SCT
- Central laboratory assessments; samples for the following to be collected within 7 days after eligibility confirmation and before leukapheresis:
  - Anti-KITE-222 CAR antibodies (serum)
  - Levels of key analytes including cytokines (serum)
  - KITE-222 CAR T cells for pharmacokinetic baseline, CCI [redacted]
  - CBC with differential (blood)

  CCI [redacted]
- Leukapheresis; refer to the IPM for details about the leukapheresis procedure, packaging, and shipment of apheresis product to the manufacturing facility.
- AE/SAE reporting; refer to Section 8.5 for safety reporting guidelines (may be performed the day before leukapheresis, unless otherwise specified).
- Concomitant medications documentation; refer to Section 6.3.12 (may be performed the day before leukapheresis, unless otherwise specified).

CCI [redacted]

[redacted] CCI

CCI

[redacted]

[redacted]

[redacted]

CCI

[redacted]

CCI [redacted]

7.6.3. Lymphodepleting Chemotherapy

CCI [redacted] before administration of KITE-222, subjects will receive a nonmyeloablative lymphodepleting chemotherapy regimen consisting of cyclophosphamide and fludarabine to induce lymphocyte depletion and create an optimal environment for the expansion of KITE-222 CAR T cells in vivo.

Subjects will receive the following CCI [redacted]

[redacted]

Any consideration for changes in the conditioning chemotherapy must be discussed with the Kite medical monitor.

Lymphodepleting chemotherapy will be supplied by the investigative site unless otherwise noted. Refer to the current product label for guidance on the packaging, storage, preparation, administration, and toxicity management associated with the administration of chemotherapy agents.

7.6.3.1. Requirements for Initiating Lymphodepleting Chemotherapy

Administration of KITE-222 cells to subjects with ongoing infection or inflammation, even if subjects are asymptomatic, may increase the risk of high-grade and fatal toxicity. All efforts should be made to rule out such conditions before administration of both lymphodepleting chemotherapy and KITE-222 infusion. If any of the following criteria are met before the initiation of lymphodepleting chemotherapy, the medical monitor must be consulted and the workup listed in Section 7.7.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within the 72 hours before the lymphodepleting chemotherapy
- Both CRP > 100 mg/L and an increase of 10% from the screening value at any time between enrollment through the start of lymphodepleting chemotherapy

Additionally:

- All eligibility criteria of the protocol must be met except: the requirement for cytopenia thresholds (described in inclusion criterion 8) and the requirement for a morphological disease in the post-bridging assessment (described in inclusion criterion 3). If any other screening assessments or procedures are repeated between confirmation of study eligibility and the start of lymphodepleting chemotherapy and the results are outside of the eligibility criteria listed in Section 4.2 (and exceeding 5% of the laboratory test value cutoffs noted in the inclusion criteria), then the condition must resolve before proceeding with lymphodepleting chemotherapy.
- In subjects who receive bridging therapy, an additional BM sample must have been collected between the end of bridging therapy and initiation of lymphodepleting chemotherapy to ensure morphologic disease, regardless of whether there is evidence of disease by circulating peripheral blasts.
- A complete history and physical examination including the head, eyes, ears, 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 the 48 hours before lymphodepleting chemotherapy (prophylactic use of antimicrobials is allowed).

- A treatment course of any antimicrobials given for a known or suspected antecedent infection should be complete as per infectious disease consult recommendation (if applicable) 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).

- The 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, or imaging studies) must be negative. If there is clinical suspicion of an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for the cultures to become positive.

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

7.6.3.2. Administration of Lymphodepleting Chemotherapy

The following assessments/procedures will be completed[redacted] at the time points outlined in the SOA (Table 10):

- Physical examination

- Vital signs

- ECOG performance status (to be assessed before initiation of chemotherapy)

- Local laboratory assessments (samples to be drawn before the initiation of the lymphodepleting chemotherapy)

  — Chemistry panel (serum)

  — Coagulation (plasma)

  — CBC with differential and percentage of blasts (blood)

  — CRP, ferritin, and LDH (serum)

  — EU sites (within 7 days before lymphodepleting chemotherapy): β-hCG pregnancy test (serum or urine) on all females of childbearing potential

- Central laboratory assessments (to be collected before the initiation of lymphodepleting chemotherapy):
  - Levels of key analytes including cytokines (serum)
  - CLL-1 expression (blood)
  - CBC with differential (blood)
- Lymphodepleting chemotherapy administration
- AE/SAE reporting (refer to Section 8.5 for safety reporting guidelines)
- Concomitant medications documentation (refer to Section 6.3.12)

Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy. In general, subjects should be kept well hydrated but closely monitored to prevent fluid overload.

7.7. Treatment Period

The assessments and procedures to be performed during the treatment period will be according to the schedule presented in the SOA (Table 10).

All subjects will be hospitalized during the treatment period, from before KITE-222 infusion (Day 0) for a recommended 28 days (minimum of 14 days) after treatment (Day 14) to monitor for signs and symptoms of infectious complications related to agranulocytosis, CRS, and neurologic toxicities. Subjects should be instructed to remain within proximity of the clinical study site until complete count recovery or transition to allo-SCT conditioning, at which time subjects should follow the institutional guidelines regarding proximity to the treating facility.

Subjects must be hospitalized from infusion (Day 0) until Day 14 at a minimum. From Day 14, subjects may be evaluated for discharge and considered for outpatient follow-up if toxicities have returned to Grade 1, have resolved, returned to baseline, or are deemed clinically insignificant by the investigator (eg, renal insufficiency that is improving). Assessments detailed in the SOA (Table 10) can be obtained on an outpatient basis, including CBC, if KITE-222-related Grade 4 neutropenia persists.

Subjects should remain hospitalized for ongoing KITE-222-related fever, hypotension, hypoxia, or ongoing neurologic toxicities with a severity of greater than Grade 1, or if deemed necessary by the investigator.

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of KITE-222. Catheter care, per institutional guidelines, should be followed.

KITE-222 is a subject-specific product and the product must not be infused if the information on the subject-specific label does not match the intended subject's information (eg, the initials and subject ID number). The volume of KITE-222 infused, the thaw start/stop time, and KITE-222

administration start and stop time must all be noted in the subject's medical record. The product must not be thawed until the subject is ready for the infusion.

The materials and instructions for the thawing, timing, and administering of KITE-222 are outlined in the IPM. The IPM must be reviewed before administration of KITE-222. Research sites should follow institutional guidelines for the infusion of cell products.

7.7.1. Requirements for KITE-222 Infusion

If any of the following criteria are met before initiation of KITE-222 infusion, the medical monitor must be consulted and the workup listed in Section 7.7.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within the 72 hours before KITE-222 infusion
- Both CRP > 100 mg/L and an increase of 10% from the screening value at any time between enrollment to the start of KITE-222 infusion

Additionally:

- All eligibility criteria of the protocol must be met except: the requirement for cytopenia thresholds (described in inclusion criterion 8) and the requirement for a morphological disease in the post-bridging assessment (described in inclusion criterion 3). Laboratory test values can also be within 5% of the cutoffs noted in the inclusion criteria. If any other screening assessments or procedures are repeated between confirmation of study eligibility and the start of KITE-222 infusion and results are outside of the eligibility criteria listed in Section 4.2 (and exceeding 5% of the laboratory test value cutoffs noted in the inclusion criteria), then the condition must resolve before proceeding with KITE-222 infusion (except for peripheral blood cell counts that have been impacted by lymphodepleting chemotherapy).
- A complete history and physical examination, including HEENT and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems, must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within the 48 hours before the infusion of KITE-222 (prophylactic use of antimicrobials is allowed).
- A treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult recommendation (if applicable) 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 an infectious disease service (if applicable).

- The 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, or imaging studies) must be negative. If there is clinical suspicion of 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, the subject can then proceed with the administration of KITE-222, following procedures described in Section 7.7.2 and Section 7.7.3.

If the KITE-222 infusion is delayed > 2 weeks, the protocol guidelines should be followed regarding the need for repeat lymphodepleting chemotherapy (refer to Section 7.6.3).

7.7.2. KITE-222 Premedications (Day 0)

The following premedications should be administered CCI [redacted] before KITE-222 infusion. Alternatives to the recommendations below should be discussed with the Kite medical monitor:

[redacted]

[redacted]

7.7.3. KITE-222 Infusion (Day 0) and After (Days 1 to 13, Day 14 [Week 2], Days 15 to 27, and Day 28 [Week 4])

The following assessments and procedures are to be completed on the day of KITE-222 administration, and on additional days during the treatment period as outlined in the SOA (Table 10):

- Physical examination
- Vital signs during and after study treatment and then routinely during hospitalization per institutional guidelines
- ECOG performance status
- Neurologic assessment (refer to the SOA [Table 10] for frequency)
- Samples for the following local laboratory assessments should be drawn before the KITE-222 infusion on Day 0 (refer to the SOA [Table 10, Table 11, and Table 12] for frequency during the treatment period)
  - Chemistry panel (serum)
  - Coagulation (plasma)
  - CBC with differential, including percentage of blasts (blood)

  - Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course regarding CRS/neurologic events. It is therefore recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continuing through Day 7. In addition, LDH should be monitored as clinically indicated.

- Central laboratory assessments (refer to the SOA [Table 10, Table 11, and Table 12] for frequency during the treatment period):
  - Anti-KITE-222 CAR antibodies (serum)
  - Key analytes including cytokines (serum):
    - As applicable, an additional serum sample for assessment of levels of key analytes, including cytokines, should be drawn at the first onset and first re-occurrence of any Grade 2 or higher CRS (refer to Section 8.3.1.1 for information on CRS grading) if not already collected on that day.

CCI [redacted]

  - CBC with differential (blood)
  - CLL-1 expression (blood)

- Lumbar puncture:
  - Lumbar puncture is recommended for subjects with a new onset of clinically significant neurologic toxicities of severity Grade 2 or higher after KITE 222 infusion, unless contraindicated (refer to Section 6.3.11).

- Disease Assessments (see Section 6.4) including BM evaluation (see Section 6.4.1) and extramedullary disease assessment (only for subjects with non-CNS extramedullary disease)
- KITE-222 premedications on Day 0 (refer to Section 7.7.2)
- Infusion of KITE-222
- AE/SAE reporting (refer to Section 8.5 for safety reporting guidelines)
- Concomitant medications documentation (refer to Section 6.3.12)

7.7.4. Monitoring After KITE-222 Infusion

Subjects must be hospitalized from infusion (Day 0) until Day 14 at a minimum. From Day 14, subjects may be evaluated for discharge and considered for outpatient follow-up if toxicities have returned to Grade 1, have resolved, returned to baseline, or are deemed clinically insignificant by the investigator (eg, a renal insufficiency that is improving). Assessments

detailed in the SOA (Table 10) can be obtained on an outpatient basis, including CBC, if KITE-222-related Grade 4 neutropenia persists. Subjects should remain hospitalized for ongoing KITE-222-related fever, hypotension, hypoxia, or ongoing neurologic toxicities with a severity of greater than Grade 1, or if deemed necessary by the treating investigator.

Subjects should be instructed to remain within proximity of the clinical study site until allo-SCT, at which time the subject should follow institutional standards regarding proximity to the clinical site. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphagia, 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.

Refer to Sections 5.5 and 5.6 for descriptions of medications that should not be taken before and after KITE-222 infusion.

7.7.5. Requirements for Workup for 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 before administration of lymphodepleting chemotherapy and/or KITE-222 consists of the following:

- Consult the Kite medical monitor
- Infectious disease service consult (if available)
- Perform CT imaging of the chest with IV contrast. CT imaging of the abdomen and pelvis with IV contrast should also be considered as clinically indicated. If there is a medical contraindication to contrast, then non-contrast CT is allowed. Refer to Secction 12.4 for country-specific requirements.
- The following must be performed (before initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic × 2 bottles each), 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, and metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, Fungitell®)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus [CMV])

- If a CNS process is suspected, then appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed.

- Any additional sign or symptom-directed investigation should be performed as clinically indicated.

Before proceeding with lymphodepleting chemotherapy and/or KITE-222 infusion, the above workup must not suggest the presence of an active infection and all requirements for lymphodepleting chemotherapy and/or KITE-222 infusion must be satisfied. If the KITE-222 infusion is delayed for more than 2 weeks following lymphodepleting chemotherapy, protocol guidelines should be followed regarding the need for repeat lymphodepleting chemotherapy (refer to Section 7.6.3).

If the above workup was triggered due to both CRP > 100 mg/L and an increase of 10% from the screening value, CRP testing should be repeated. If CRP continues to increase significantly, an evaluation should be performed for any other potential infectious or inflammatory condition that was not previously evaluated.

7.8. Post-treatment Follow-up Period

7.8.1. Post-treatment Follow-up Assessment Visits

Assessments and procedures to be performed during the post-treatment assessment period will be according to the schedule presented in the SOA (Table 10).

After completing KITE-222 infusion and after being discharged from the hospital, all subjects will be followed during the post-treatment assessment period. Counting from Day 0 (day of KITE-222 infusion), subjects will return to the clinic for an evaluation at the following time points:

- Week 5, Day 35 (± 3 days; for subjects who have not initiated conditioning chemotherapy for allo-SCT)

- Week 6, Day 42 (± 3 days; for subjects who have not initiated conditioning chemotherapy for allo-SCT)

- Week 7, Day 49 (± 3 days; for subjects who have not initiated conditioning chemotherapy for allo-SCT)

- Month 2 (± 1 week; for subjects who have not initiated conditioning chemotherapy for allo-SCT)

- Month 3 (± 1 week; for subjects who have not initiated conditioning chemotherapy for allo-SCT)

- Within one week before the conditioning chemotherapy for allo-SCT is initiated (if applicable)

- One day before the allo-SCT is administered (if applicable)

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

The following procedures are to be completed for subjects as outlined in the SOA (Table 10):

- Physical examination
- Vital signs
- Neurologic assessment (refer to Section 6.3.8)
- Local laboratory assessments for the following:
  - Chemistry panel (serum)
  - Coagulation (plasma)
  - CBC with differential, including percentage of blasts (blood)
  - β-hCG pregnancy test (serum or urine) on all females of childbearing potential
- Central laboratory assessments for the following:
  - Anti-KITE-222 CAR antibodies (serum)
  - Key analytes including cytokines (serum)
  - KITE-222 CAR T cells, CCI [redacted]
  - CBC with differential (blood)
  - CLL-1 expression (Blood)
  - As applicable, an additional sample for assessment of levels of key analytes including cytokines (serum) and KITE-222 T cells (PBMCs) should be drawn at the first onset and first re-occurrence of any Grade 2 or higher KITE-222-related toxicity, such as Grade 2 CRS or neurologic event, and upon resolution of the event, if not already collected on that day.
- Disease assessment (refer to SOA [Table 10]), including BM evaluation (see Section 6.4.1) and extramedullary disease assessment (only for subjects with non-CNS extramedullary disease)
- AE/SAE reporting (refer to Section 8.5 for safety reporting guidelines)

- Concomitant medications documentation (refer to Section 6.3.12)

If a subject is readmitted to the hospital with any KITE-222-related AE after the initial hospitalization for the KITE-222 infusion, the following samples will be collected on the day of admission, then weekly, and on the day of discharge; samples will be sent to the central laboratory:

- Key analytes (including cytokines) (serum)
- KITE-222 CAR T cells (PBMCs)

7.8.2. Evaluation Visit at the Time of Disease Progression or Relapse

If a subject's disease progresses or the subject experiences a relapse before completion of allo-SCT, the procedures listed below will be completed. If disease progression is identified at a scheduled visit, the assessments scheduled for that visit will be performed in addition to any additional disease assessment or other procedures listed below; if necessary, some of these procedures can be performed at an additional unscheduled visit. If disease progression or relapse is identified between the scheduled visits, the subject will be asked to attend an unscheduled visit for disease assessment and procedures listed below.

The following assessments/procedures are to be completed at the time of disease progression or relapse (also identified in Table 11 and Table 12):

- CCI [redacted]
- Physical examination
- Vital signs
- Local laboratory assessments (if not already collected at visit in which progressive disease/relapse was confirmed) for the following:
  - CBC with differential, including percentage of blasts (blood)
- Central laboratory assessments for the following:
  - Key analytes, including cytokines (serum) to be collected at the time point that disease progression was identified and before the subject initiates subsequent anticancer therapy
  - CCI [redacted]
  - CLL-1 expression (blood)
  - Anti-KITE-222 CAR antibodies (serum)

— CBC with differential (blood)

- AE/SAE reporting (refer to Section 8.5 for safety reporting guidelines)
- Concomitant medications documentation (refer to Section 6.3.12)

Refer to Section 7.9.2 for information on follow-up for subjects whose disease progresses or relapses after receiving KITE-222.

7.9. Follow-up Period (After Month 3 Post-treatment Until Transition to LTFU Study)

Assessments and procedures to be performed during the follow-up period will be according to the schedule presented in the SOA (Table 11 and Table 12).

As described in Section 3.4 and Section 3.5, after completing at least 24 months of assessments in this study, all subjects who received an infusion of KITE-222 will be transitioned to a separate LTFU study, after providing informed consent. Until this timepoint, subjects will complete the post-treatment follow-up visits within this protocol per the SOA Table 11 and Table 12 and the descriptions below. Subjects will begin the follow-up period after they have completed the Month 3 visit of the post-treatment follow-up period (whether they have responded to treatment or went straight to follow-up due to disease progression). The follow-up period will include the following visits for subjects who do not proceed to allo-SCT:

- Month 6 through Month 18 after the infusion of KITE-222, every 3 months (± 2 weeks)
- Month 18 through Month 24 after the infusion of KITE-222, every 6 months (± 1 month)
- Month 24 until up to Month 60 after the infusion of KITE 222, every 12 months (± 1 months)
- Month 60 until up to 15 years after the infusion of KITE-222, every 12 months (± 3 months)

The follow-up period will include the following visits for subjects who proceed to allo-SCT (calculated from the day of allo-SCT unless otherwise specified):

- Month 1 (± 3 days)
- Month 3 through Month 18, every 3 months (± 2 weeks)
- Month 24 to 15 years after the infusion of KITE-222, every 12 months (± 3 months)
- At relapse post allo-SCT disease assessment

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

Subjects who are unable or unwilling to return to the study site may have post-treatment follow-up data for this period obtained from clinical, laboratory, and/or diagnostic assessments conducted by the referring HCP and/or GP. In addition, other health status information may be obtained from the subject and/or the subject's referring HCP and/or GP via telephone or email communication. This information will be used to detect late-onset targeted AEs and SAEs that may be related to KITE-222.

Subjects and/or the subject's referring HCP and/or GP may be contacted directly by telephone or email to confirm survival status and obtain information about targeted concomitant medication use, subsequent anticancer therapy, and late-onset targeted AEs/SAEs (if the SAE does not require a test to be performed in the clinic).

7.9.1. Follow-up Assessments and Procedures for Enrolled Subjects Who Received KITE-222

The following assessments/procedures are to be completed at the time points indicated in the SOA (Table 11 and Table 12) for enrolled subjects who received KITE-222, regardless of whether they did or did not undergo an allo-SCT:

- Physical examination
- Disease assessment (refer to Section 6.4 and the SOA [Table 11 and Table 12]).
  - Disease assessment will be performed per the SOA through Month 24 or until disease progression or relapse, whichever occurs first.
  - If the subject's disease has not progressed by Month 24, disease assessments will be performed per standard of care after Month 24.
- Local laboratory assessments of CBC with differential (blood) is not required after disease progression.
- Central laboratory assessments for the following:
  - CBC with differential and inflammatory markers (blood)
  - Anti-KITE-222 CAR antibodies (serum)
  - KITE-222 CAR T cells, CCI [redacted]
  - CLL-1 expression (blood)
- Targeted AE reporting (refer to Section 8.5.1.1; not required after disease progression)
- Targeted SAE reporting (refer to Section 8.5.1.2 for safety reporting guidelines)

- Reporting of all KITE-222-related SAEs and any deaths, regardless of causality
- Targeted concomitant medication documentation (refer to Section 6.3.12)
- Subsequent anticancer therapy for the treatment of AML (refer to Section 7.12)
- Survival status: Subjects may be contacted by telephone to confirm their survival status

7.9.2. Follow-up Procedures for Enrolled Subjects Whose Disease Progressed After KITE-222 Treatment

The following procedures/assessments are to be completed at the time points outlined in the SOA (Table 10, Table 11, and Table 12) for enrolled subjects whose disease progressed after KITE-222 treatment:

- Local laboratory assessments of the DLT window period up to Week 4 as per Table 10, if possible
- Disease assessment per standard of care
- Survival status: Subjects may be contacted by telephone to confirm their survival status
- Subsequent anticancer therapy for the treatment of AML (refer to Section 7.12)
- AE/SAE reporting until 30 days after last procedure (eg, leukapheresis, lymphodepleting chemotherapy) (refer to Section 8.5 for safety reporting guidelines)
- Concomitant medication documentation until 30 days after the last study-specific procedure has occurred (eg, leukapheresis, lymphodepleting chemotherapy) or until the initiation of new anticancer therapy, whichever occurs first (refer to Section 6.3.12)
- Targeted SAE reporting for secondary malignancies (refer to Section 8.5.1.2)
- CCI [redacted]
- CCI [redacted]

7.9.3. Procedures for Enrolled Subjects Who Were Not Treated With KITE-222

The following procedures/assessments are to be completed for enrolled subjects who were not treated with KITE-222:

- AE/SAE reporting until 30 days after last procedure (eg, leukapheresis, lymphodepleting chemotherapy) (refer to Section 8.5 for safety reporting guidelines)

- Concomitant medication documentation until 30 days after the last study-specific procedure has occurred (eg, leukapheresis, lymphodepleting chemotherapy) or until the initiation of new anticancer therapy, whichever occurs first (refer to Section 6.3.12)

For subjects who are enrolled but not dosed, the end of the study will be 30 days after the last procedure has been completed.

7.10. Retreatment

Retreatment with KITE-222 is not allowed.

7.11. Poststudy Care

Kite will not provide additional care for study subjects after their participation in the study has ended.

7.12. Subsequent Anticancer Therapy

Subsequent anticancer therapy (apart from allo-SCT) should not be administered except where disease progression has been documented and confirmed. Subsequent anticancer therapy refers to treatment administered after KITE-222 infusion that is necessary to treat a subject's disease, such as non-study-specified chemotherapy, immunotherapy, targeted agents, radiation therapy, and other investigational agents.

Subsequent anticancer therapy administered after KITE-222 infusion for a subject's disease will be recorded in eCRFs for all enrolled subjects until one of the following occurs: subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled, but do not receive KITE-222 infusion, information about any additional anticancer therapy will also be collected until the subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or dies.

7.13. Instructions for Follow-up and Data to Be Collected for Subjects Withdrawn From Study

If partial withdrawal of consent occurs (defined in Section 4.3), the investigator must discuss with the subject the appropriate process for continued participation, completion of procedures, and the associated data collection as outlined in the SOA (Table 10, Table 11, and Table 12).

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.

If withdrawal of full consent occurs (defined in Section 4.3), the investigator must discuss with the subject appropriate procedures for withdrawal from the study. Subject data collected up to full withdrawal of consent will be retained and included in the analysis of the study, and where permitted by local regulations, publicly available data (eg, death records) can be included after withdrawal of consent.

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

7.14. Sample Storage

CCI [redacted]. Each subject will have the right to have their 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 ID 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 will be entered in the study database.

8. ADVERSE EVENTS AND TOXICITY MANAGEMENT

8.1. Definitions of AEs and SAEs

8.1.1. AEs

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

The definition of an AE includes a 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, 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) must be provided.

An AE does not include the following:

- 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 study-mandated procedures, or hospitalization as a precautionary measures per institutional policy are not considered AEs (refer also to Section 8.4).

- The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods is not considered to be an AE. Worsening of signs and symptoms of the malignancy under study are considered to be AEs.

Refer to Section 8.5.1 for information and instructions for recording and reporting AEs. Refer to Section 8.5.3 for information and instructions for recording and reporting AEs due to disease progression.

8.1.2. DLTs

DLTs are defined as the following KITE-222-related events with an onset within the first 28 days after the KITE-222 infusion unless otherwise specified:

- Grade 5 event

- Grade 4 CRS of any duration or Grade 3 CRS not improving to Grade 2 or less within 72 hours

- Grade 3 or higher cardiac and/or pulmonary events are DLTs unless the events:
  - Are related to CRS and improve to Grade 2 or less within 72 hours
  - Can be managed with appropriate noninvasive supportive care (eg, cough, atelectasis, dyspnea) that resolves to baseline by Day 28
- Grade 4 ICANS or other Grade 4 AEs associated with neurologic events
- Grade 3 ICANS
  - Exception: Grade 3 ICANS with grading based only on ICE score and/or depressed level of consciousness that improves to Grade 2 or less within 72 hours
- Grade 3 or higher infusion or immediate hypersensitivity reaction
- Ongoing Grade 4 neutropenia or thrombocytopenia that is not due to leukemia persistence by Day 42 for subjects who have not started the conditioning regimen for an allo-SCT
- All other KITE-222 related Grade 3 non-hematologic AEs lasting more than 7 days, and all KITE-222-related Grade 4 non-hematologic AEs. The following exceptions are not considered DLTs:
  - Grade 3 or 4 fever
  - Grade 3 febrile neutropenia returning to baseline within 2 weeks or Grade 3 infection that resolves to Grade 2 or less within 2 weeks
  - Renal toxicity, including the need for dialysis, improving to Grade 2 or lower in ≤ 7 days
  - TLS including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, or hyperuricemia)
  - Grade 4 AST, ALT, alkaline phosphatase, bilirubin, or other liver function test elevation, provided there is resolution to severity of Grade 2 or lower within 7 days
  - Grade 3 nausea and/or anorexia

As noted in Section 8.7, CRS and ICANS will be graded according to a revised grading system {Lee 2019}. AEs attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT. AEs attributed to ICANS will be mapped to the overall ICANS grading assessment for the determination of a DLT. The severity of individual signs/symptoms of CRS and ICANS will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 for those signs/symptoms that are not part of the grading scale.

8.1.3. SAEs

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

- Fatal
- Life threatening (ie, an event that places the subject at an immediate risk of death; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization (refer to Section 8.4 for the definition of prolongation of planned hospitalization for this study)
  - An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility and occurs outside of the recommended 28-day hospitalization.
  - 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 or if that event resulted in a prolongation of the existing planned hospitalization.
  - Refer to Section 8.4 for hospitalizations that are not considered as SAEs.
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event. If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE according to the NCI CTCAE; 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.

Progression of the malignancy during the study is not considered to be an SAE; signs and symptoms of disease progression can be considered to be SAEs (and documented as being due to disease progression).

Refer to Section 8.5 for information and instructions on the recording and reporting SAEs. Refer to Section 8.5.3 for information and instructions on the recording and reporting SAEs due to disease progression.

8.1.4. Targeted AEs and SAEs

For subjects who do not receive a subsequent allo-SCT, targeted AEs and SAEs are to include neurologic, hematologic, infection, new occurrence, or aggravation of GVHD, and secondary malignancy events.

For subjects who receive a subsequent allo-SCT, targeted AEs and SAEs are to include neurologic, primary graft failure, infection, new occurrence, or aggravation of GVHD, and secondary malignancy events.

Although only secondary malignancies are considered to be targeted AEs/SAEs, all new malignancies will be reported. New malignancies are defined as the development of any new malignancies occurring after the KITE-222 infusion. A secondary malignancy is defined as a new malignancy suspected to be possibly related to KITE-222 (ie, temporally associated with KITE-222 and without compelling alternate etiologies).

Refer to Section 8.5.1.1 and 8.5.1.2 for information and instructions for recording and reporting targeted AEs and targeted SAEs, respectively.

8.2. Clinical Laboratory and Vital Sign Abnormalities

8.2.1. Abnormal Clinical 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 an adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as an 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:

- Is 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
- Is clinically significant in the investigator's judgment

8.2.2. 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:

- Is accompanied by clinical symptoms

- Results in a medical intervention or a change in concomitant therapy
- Is 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 eCRF.

8.3. Assessments of AE and SAE Severity and Causality

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of the accuracy of the event information and assessments.

8.3.1. Assessment of AE/SAE Severity

The severity of AEs will be graded according to the NCI CTCAE version 5. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program home page (http://ctep.cancer.gov).

8.3.1.1. Grading of CRS and Neurologic Events

The severity of CRS and ICANS events will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading {Lee 2019}. Copies of the ASTCT CRS and ICANS grading scales can be downloaded from (http://tgapp.asbmt.org). The severity of individual signs/symptoms of CRS and neurologic events will be graded according to the NCI CTCAE version 5.0 for those signs/symptoms that are not part of the grading scale. Refer to the current IB for details on toxicity management and CRS grading.

8.3.2. Assessment of AE/SAE Relationship to IP and Study Procedures

When reviewing AEs, investigators must assess whether the AE is possibly related to 1) the IP (KITE-222), 2) leukapheresis, 3) bridging therapy, 4) lymphodepleting chemotherapy, or 5) any protocol-required study procedure. The relationship is indicated by a "related" or "not related" response and entered in the eCRF. When assessing causality, the investigator or qualified subinvestigator will use clinical judgment and the following considerations:

- Not Related: There is evidence that the AE has an etiology other than the IP or study procedure. For SAEs, an alternative causality must be provided (eg, disease progression, concurrent disease[s], concomitant medications, or other).
- Related: There is a reasonable possibility that the event may have been caused by the IP or as a result of a study procedure.

8.4. 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 8.5.1.2. Hospitalization is considered prolonged when a subject is hospitalized for > 28 days after the infusion of KITE-222 with the exception of extended hospitalization for a planned allo-SCT.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative care or hospice care
- Planned hospitalization required by the protocol (eg, for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization for Grade 4 or lower hematologic toxicity < 42 days after the KITE-222 infusion
- Hospitalization for an allo-SCT
- Hospitalization due to the progression of the underlying cancer (refer to Section 8.5.3 for instructions on reporting of the signs/symptoms of the underlying malignancy or disease progression as AEs or SAEs.)

8.5. Investigator Requirements and Instructions for Reporting AEs, SAEs, and Deaths to the Sponsor

8.5.1. Reporting AEs and SAEs

The investigator or qualified subinvestigator must address the below for AEs/SAEs:

- AE diagnosis or syndrome (or, if not known, signs or symptoms)
- Dates of the onset and resolution
- Severity (Section 8.3.1)
- Assessment of relatedness to KITE-222, lymphodepleting chemotherapy, or study procedures (Section 8.3.2)
- Action taken

Additional relevant data with respect to describing the AE/SAE will be collected in the eCRFs. For AEs/SAEs, a diagnosis (if known) rather than the individual signs and symptoms should be recorded on the eCRF AE form. The exception is for CRS where both the diagnosis and significant signs and symptoms will be captured on the eCRF AE form.

The investigator is expected to follow the reported AEs/SAEs 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.

Refer to Section 8.5.3 for instructions on reporting AEs/SAEs associated with disease progression.

The investigator's clinical judgment will be used to determine whether a subject is to be removed from the study treatment due to an AE/SAE. In the event a subject requests to withdraw from protocol-required therapies or the study due to an AE/SAE, the subject should undergo the procedures outlined in the Month 3 visit of the SOA (Table 10).

Refer to Section 8.5.1.1 and Section 8.5.1.2 for additional information on reporting AEs and SAEs, respectively.

8.5.1.1. Reporting AEs

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject during the AE-reporting period, as described in Table 7. Refer to Section 8.5.3 for instructions on reporting AEs associated with disease progression.

Table 7. Reporting Requirements for AEs

Subjects Who Are Enrolled, but Do Not Receive KITE-222 Infusion	**Subjects Who Are Enrolled and Receive KITE-222 Infusion**
AEs that occur from enrollment (ie, commencement of leukapheresis) through 30 days after the last study-specific procedure (eg, leukapheresis, bridging therapy, lymphodepleting 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 KITE-222 infusion or until initiation of another anticancer therapy, whichever occurs first, are to be monitored and reported.
	In subjects who do not receive a subsequent allo-SCT, after 3 months, only targeted AEs will be reported through 24 months after KITE-222 infusion or until disease progression or relapse, whichever occurs first, and will be recorded in the eCRF. • Targeted AEs include neurological events, hematological events, infections, new occurrence or aggravation of GVHD, and secondary malignancies[a]. • Note[a]: all new malignancies are to be reported; however, only secondary malignancies are considered to be targeted AEs. All AEs deemed related to KITE-222 infusion should be recorded in the eCRF and reported regardless of study period.
	In subjects who receive a subsequent allo-SCT, only targeted AEs will be reported after the start of the conditioning regimen for the allo-SCT, through 24 months or until disease progression or relapse, whichever occurs first, and will be recorded in the eCRF. • Targeted AEs include neurological events, primary graft failure[b] events, infections, new occurrence or aggravation of GVHD, and secondary malignancies[a]. • Note[a]: all new malignancies are to be reported; however, only secondary malignancies are considered to be targeted AEs. All AEs deemed related to KITE-222 infusion should be recorded in the eCRF and reported regardless of study period.

Abbreviations: AE, adverse event; allo-SCT, allogeneic stem-cell transplantation; eCRF, electronic case report form; GVHD, graft-versus-host disease.

a. New malignancies are defined as the development of any new malignancies occurring after the KITE-222 infusion. Secondary malignancies are defined as the development of any new malignancies, with the exception of a relapse of the primary malignancy, occurring after the administration of KITE-222. Secondary malignancies will continue to be reported through 15 years after KITE-222 infusion.

b. Primary graft failure is defined as no evidence of engraftment or hematological recovery of donor cells, within the first month after transplant, without evidence of disease relapse. Engraftment is defined as the first of 3 consecutive days with an absolute neutrophil count higher than 0.5×10^9/L (sustained $>20 \times 10^9$/L platelets and hemoglobin >80 g/L, free of transfusion requirements).

8.5.1.2. Reporting SAEs

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject during the SAE-reporting periods described in Table 8. Refer to Section 8.5.3 for instructions on reporting SAEs associated with disease progression.

Table 8. Reporting Requirements for SAEs

Subjects Who Are:	
• **Screen Failures** • **Enrolled But Do Not Receive KITE-222 Infusion**	• **Enrolled and Received KITE-222 Infusion**
All SAEs that occur from signing of screening ICF through 30 days after the last study-specific procedure (eg screening procedure, leukapheresis, bridging therapy, or lymphodepleting chemotherapy) or until the initiation of a new anticancer therapy, whichever occurs first, will be recorded in the eCRF and reported.	All SAEs that occur from signing of the screening ICF through 3 months after the KITE-222 infusion or until initiation of another anticancer therapy, whichever occurs first, will be recorded in the eCRF and reported.
	In subjects who do not receive a subsequent allo-SCT, after 3 months, only targeted SAEs will be reported through 24 months after KITE-222 infusion or until disease progression or relapse, whichever occurs first, and will be recorded in the eCRF. • Targeted SAEs include neurological events, hematological events, infections, new occurrence or aggravation of GVHD, and secondary malignancies[a]. • Note[a]: all new malignancies are to be reported; however, only secondary malignancies are considered to be targeted AEs.
	In subjects who receive a subsequent allo-SCT, only targeted SAEs will be reported after the start of the conditioning regimen for the allo-SCT, through 24 months or until disease progression or relapse, whichever occurs first, and will be recorded in the eCRF. • Targeted SAEs include neurological events, primary graft failure event[b], infections, new occurrence or aggravation of GVHD, and secondary malignancies[a]. • Note[a]: all new malignancies are to be reported; however, only secondary malignancies are considered to be targeted AEs.
	After 24 months, targeted SAEs of secondary malignancies[a] will continue to be reported through 15 years after KITE-222 infusion and will be recorded in the eCRF.
	All SAEs deemed related to KITE-222 infusion should be recorded in the eCRF and reported regardless of study period.
	All deaths that occur from signing of the screening ICF. Refer to Sections 8.5.2 and 8.5.3 for instructions on reporting deaths.

Abbreviations: AE, adverse event; allo-SCT allogeneic stem-cell transplantation; eCRF, electronic case report form; GVHD, graft-versus-host disease; ICF, informed consent form; SAE, serious adverse event.

a. New malignancies are defined as the development of any new malignancies occurring after the KITE-222 infusion. Targeted SAEs of secondary malignancies will be reported during the entire reporting period (ie, through 15 years after KITE-222 infusion) for all subjects, including those whose disease progresses. Secondary malignancies are defined as the development of any new malignancies, with the exception of a relapse of the primary malignancy, occurring after the administration of KITE-222.
b. Primary graft failure is defined as no evidence of engraftment or hematological recovery of donor cells, within the first month after transplant, without evidence of disease relapse. Engraftment is defined as the first of 3 consecutive days with an absolute neutrophil count higher than 0.5×10^9/L (sustained $>20 \times 10^9$/L platelets and hemoglobin >80 g/L, free of transfusion requirements).

Unless otherwise indicated in Table 8:

- The following must be submitted to Kite via the electronic SAE (eSAE) system within 24 hours after the investigator's knowledge of the event:
  - All SAEs
- The following events must be submitted as SAEs via the eSAE system within the 24 hours after the investigator's knowledge of the event:
  - CRS events Grade 3 or higher
  - ICANS events Grade 3 or higher
  - All events of cerebral edema
  - All events of HLH/macrophage activation syndrome

If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the paper SAE Report Form and sent via email to the SAE Reporting mailbox at Safety_FC@gilead.com. Subsequently, SAEs will be entered into the eSAE system once it becomes available. All SAEs will be reported to the health authorities per local reporting guidelines.

8.5.2. Reporting Deaths

Death must be reported if it occurs during the SAE-reporting period, irrespective of any intervening treatment. Refer to Section 8.5.3 for instructions on reporting deaths associated with the underlying malignancy/disease progression.

Any death occurring after signing of the ICF and within 3 months after the KITE-222 infusion or until the conditioning chemotherapy for allo-SCT (whichever is shorter), regardless of attribution to treatment, requires expedited reporting within 24 hours of the event. Any death occurring after the 3-month SAE-reporting period requires expedited reporting within 24 hours only if it is considered related to treatment, KITE-222 infusion, and/or study-required treatments (eg, lymphodepleting chemotherapy).

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 eCRF AE form with entries including the start date of the event and the death date as the stop date of the event. Every effort should be made to capture the established cause of death, which may become available later on (eg, after an autopsy).

8.5.3. Reporting AEs, SAEs, and Deaths Associated With Disease Progression or Relapse

Progression or relapse of AML ("disease progression") as assessed by measurement of marrow, peripheral blood or extramedullary malignant lesions, should not be reported as an AE or SAE.

For situations when an AE or SAE is due to the malignancy under investigation, the sign(s) and symptom(s), including worsening of sign(s) and symptom(s), of the malignancy under study should be reported as an AE/SAE in the appropriate section of the eCRF and the investigator should check the appropriate data field to indicate that these signs and symptoms are due to the underlying disease/disease progression.

If the malignancy has a fatal outcome within 3 months after the KITE-222 infusion, and is deemed by the investigator as the event leading to death, it must be recorded as an SAE with a CTCAE v5.0 severity of Grade 5 and outcome of "fatal". Within this 3-month period, the death that is due to the underlying disease/disease progression must be reported immediately to the sponsor as an SAE, as follows:

- If there are no signs and symptoms of alternate underlying disease associated with the death (although the death has been determined to be due to disease progression), the death should be reported immediately to the sponsor as an SAE with the primary tumor type (eg, "acute myeloid leukemia") as the event term.

- If the death is due to a sign or symptom of the underlying disease/disease progression and the sign or symptom is a targeted SAE, then the SAE will be reported as the event term. The investigator should check the appropriate eCRF data field to indicate that these signs and symptoms are due to the underlying disease/disease progression.

8.6. Sponsor Reporting Requirements (Includes Reporting of SAEs and Deaths)

Depending on the relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations (CFR), the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Kite may be required to expedite to worldwide regulatory agencies reports of serious adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Kite or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

The assessment of expectedness for SAEs will be determined by Kite using reference safety information specified in the current IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

8.7. Toxicity Management

To date, the following important identified risks have been associated with CAR therapy and are considered important potential risks for KITE-222: CRS, neurologic events, infections, cytopenias, and hypogammaglobulinemia. Refer to the current IB, Guidelines for Management of Important Risks, for details regarding these events and management guidance.

As the safety experience with KITE-222 increases, the management guidance may be updated. Therefore, it is important to always refer to the most recent version of the IB for guidance regarding the management of KITE-222 related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with KITE-222, as well as possible complications associated with malignancy and cancer treatment.

8.8. Special Situations Reports

8.8.1. Definitions of Special Situations

Special situation reports include all reports of medication error – actual or potential, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or falsified medicine, and pregnancy reports (Maternal Pregnancy and Partner Pregnancy) regardless of an associated AE.

A medication error (actual or potential) is any unintentional error in the prescribing, dispensing, preparation for administration or administration of an IP while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of an IP by a clinical study subject.

Misuse is defined as any intentional and inappropriate use of an IP that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of an IP (eg, lymphodepleting chemotherapy or other study-specified IP) given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, an overdose will be established only when it is clear that the subject has

taken the excess dose(s). An overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

An occupational exposure is defined as exposure to an IP as a result of one's professional or non-professional occupation.

A drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

An unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Kite IP.

Counterfeit or falsified medicine is defined as any IP with a false representation of: a) its identity, b) its source, or c) its history.

8.8.2. Instructions for Reporting Special Situations

8.8.2.1. Instructions for Reporting Pregnancies

Any pregnancy in a female subject enrolled into the study must be reported, regardless of the time after KITE-222 infusion. If the pregnancy occurs in a female partner of a male subject within 12 months after completing lymphodepleting chemotherapy or the administration of KITE-222, 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 Safety_FC@gilead.com or fax: +1 (650) 522-5477.

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 KITE-222 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 forms within 24 hours after

becoming aware of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Patient Safety and Pharmacovigilance.

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

8.8.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the Special Situations Reporting Form and forwarded to Kite Patient Safety and Pharmacovigilance within 24 hours after the investigator becomes aware of the situation. These reports must consist of situations that involve study drug and/or Kite concomitant medications, but do not apply to non-Kite concomitant medications.

Special situations involving non-Kite concomitant medications do not need to be reported on the special situations report form; however, special situations that result in AEs due to a non-Kite concomitant medication, must be reported as an AE.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome of the AEs or SAEs will be reported, when available. Refer to Section 8.8.2.1 and the eCRF completion guidelines for instructions on special situation reporting.

8.9. Safety Review Team

The SRT is comprised of the Kite medical monitor, drug safety physician, study statistician, and at least 1 active study investigator. The SRT will be specifically chartered to review the safety data during this Phase 1 study. The SRT will assess DLTs in the dose-escalation part and AEs throughout the study. Additional SRT oversight includes ensuring the correct interpretation of the 3 + 3 design on dose escalation or de-escalation decisions, assessing criteria to pause enrollment for safety issues, confirming the optimal dose of KITE-222 for use with the expansion cohort and adding or adjusting the dose cohorts in the dose-escalation part. Furthermore, the SRT will meet after the sixth subject in the expansion cohort has been dosed and followed for 28 days to continue in-depth monitoring of AEs and SAEs. The SRT will meet at least once for each dose-escalation cohort and Ad Hoc throughout the course of the study to address emerging safety or study conduct concerns.

The SRT recommendations will be formally communicated to the participating sites.

8.10. Criteria to Pause or Stop Enrollment

As part of its oversight of the study, the SRT will assess the criteria to pause or stop enrollment.

Enrollment will be paused or stopped if the following KITE-222-related AEs are observed:

- After approximately 14 subjects have been treated with KITE-222 and have had the opportunity to be followed for 21 days, the incidence of Grade 4 CRS is greater than 25%
- Any new malignancy (ie, a malignancy that is not recurrence/progression of the previously treated malignancy) that is possibly related to KITE-222
- Any life-threatening (Grade 4) toxicity attributable to KITE-222 that is unmanageable and not described as a potential risk in the IB or seen in the underlying disease
- Any Grade 4 or higher infections related to KITE-222 or lymphodepleting chemotherapy
- Any Grade 4 infusion reaction/hypersensitivity
- Any Grade 4 cardiac event
- Any Grade 4 neurologic toxicity
- Any Grade 5 SAE after KITE-222 infusion at least possibly related to KITE-222

The appropriate regulatory authorities will be notified within the applicable safety reporting timelines if any of these stopping or pausing rules occur. Accrual will be resumed upon the recommendation of the SRT.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Analysis Plan

An overview of the statistical analysis plan (SAP) is provided below. Details will be provided in the SAP.

9.2. Hypothesis

No formal hypothesis will be tested in this Phase 1 study.

9.3. Determination of Sample Size

The anticipated enrollment in this study should allow for having 40 subjects treated; up to 18 subjects will be enrolled in the dose-escalation part and 22 subjects will be the target number for enrollment in the expansion cohort. Refer to Section 3.2 for more details on the study design.

With a total sample size of 28 subjects at the selected dose level, an observed CCR rate of 50% (14 of 28 subjects) will yield an exact 95% confidence intervals (CIs) of 31% and 69%. Additional assumptions and corresponding 2-sided 95% exact CIs are provided in Table 9.

Table 9. Exact 95% Confidence Intervals Corresponding to Composite Complete Remission Rate

Subjects with CCR	Observed CCR Rate*	95% Confidence Interval
10	36%	[19%, 56%]
12	43%	[24%, 63%]
14	50%	[31%, 69%]
16	57%	[37%, 76%]
18	64%	[44%, 81%]

Abbreviations: CCR, composite complete remission
* Total of 28 treated subjects at the selected dose level

9.4. Access to Individual Subject Treatment Assignments and Minimization of Bias

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 SAP and SRT charter.

9.5. Planned Analysis

9.5.1. Interim Analysis and Early Stopping Guidelines

Formal interim analyses of efficacy are not planned for the early trial stopping purpose.

An SRT will be chartered to review safety during the Phase 1 dose-escalation part of the study and to make recommendations on further study conduct in the Phase 1 dose-escalation cohorts.

Before the final analysis, interim analyses may be conducted and submitted to regulatory agencies to seek guidance for the overall clinical development program.

9.6. Primary Analysis

The primary analysis of the primary endpoint will be conducted when the last treated subject in the dose expansion cohort has had the opportunity to be evaluated for response 3 months after KITE-222 infusion or 1 month after allo-SCT, whichever occurs first. Additional analyses may occur after the primary analysis has been completed; these additional analyses will be descriptive.

9.6.1. Final Analysis

The final analysis will be performed after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

9.6.2. Long-term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject receives KITE-222; LTFU will be performed on subjects after the transition to the LTFU study (refer to Section 3.4 and Section 3.5).

No formal hypothesis testing will be performed on the data obtained after the data cutoff date for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

9.7. Analysis Conventions

9.7.1. Analysis Sets

The following analysis sets will be used to analyze study data:

- Full analysis set (FAS): consists of all enrolled subjects. The FAS will be used for summaries of subject disposition.

- mITT set: consists of all subjects enrolled and treated with at least 50% of the optimal dose of KITE-222 including all subjects treated in both the dose-escalation cohort and the expansion cohort. The mITT analysis set will be used for all efficacy analyses unless otherwise specified.

- DLT-evaluable set: defined for each dosing cohort in the dose-escalation part of the study, consists of subjects treated in each dose-escalation cohort who:

— Received the target dose and were followed for at least 28 days after infusion of KITE-222; or

— Received a dose of KITE-222 that was lower than the target for that cohort and experienced a DLT during the 28-day post infusion period

- Safety analysis set: consists of all subjects treated with any dose of KITE-222

9.8. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will include sex, race/ethnicity, age, disease characteristics, and will be summarized using standard descriptive methods.

9.9. Efficacy Analysis

9.9.1. Composite Complete Remission Rate

The incidence of CCR (CR + CRMRD$^-$ + CRi as defined by the ELN 2017 Classification and described in Section 12.5) and exact 2-sided 95% CIs will be generated. All subjects who do not meet the criteria for CR, CRMRD$^-$, or CRi by the analysis data cutoff date will be considered nonresponders for the overall CR rate evaluation.

9.9.2. Overall Remission Rate

The incidence of the OR rate (CR + CRMRD$^-$ + CRi + MLFS + PR as defined by the ELN 2017 Classification and described in Section 12.5) and exact 2-sided 95% CIs will be generated. All subjects who do not meet the criteria for CR, CRMRD$^-$, CRi, MLFS, or PR by the analysis data cutoff date will be considered nonresponders for the OR rate evaluation.

9.9.3. Relapse-free Survival

For subjects who experience CR, CRMRD$^-$, or CRi, RFS is defined as the time between their first CR/ CRMRD$^-$/CRi to relapse or death due to any cause. Subjects not meeting the criteria for relapse or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing. The RFS for subjects that undergo new anticancer therapies (except for allo-SCT) in the absence of a documented relapse will be censored at the last evaluable disease assessment before initiation of any new anticancer therapies. Subjects who received subsequent allo-SCT will not be censored at the last disease assessment before the allo-SCT; instead, the response after allo-SCT will contribute to the derivation of RFS.

Both hematological and molecular RFS (as defined in Section 12.5) Kaplan-Meier estimates and 2-sided 95% CIs will be generated for RFS. Estimates of the proportion of subjects in remission at 3-month intervals from the first response will be provided.

9.9.4. Allo-SCT Rate

The incidence of on study allo-SCT will be summarized by overall, subjects achieving CRMRD$^-$, and subjects achieving CR + CRi. Corresponding 2-sided 95% CIs will be generated.

9.9.5. Event-free Survival

EFS is defined as the time from the KITE-222 infusion date to the earliest date of disease relapse, progressive disease, refractory disease, or death due to any cause. Refractory disease is defined as the subject not experiencing CR, CRMRD$^-$, or CRi by the Week 6 disease assessment as defined in Section 12.5.

The following criteria will be used to further define events and event times:

- Subjects with an established CR, CRMRD$^-$, or CRi who subsequently commence new anticancer therapy (except for allo-SCT) in the absence of documented relapse will have their EFS time defined as the time from the KITE-222 infusion date to the last evaluable disease assessment prior to the new anticancer therapy.

- Subjects with best response of MLFS, PR or stable disease (SD) and who subsequently commence new anticancer therapy (including allo-SCT) in the absence of documented disease progression before the Week 6 assessment, will have their EFS time defined as the time from the KITE-222 infusion date to the disease assessment prior to the new anticancer therapy.

The following criteria will be used to further define censoring times:

- Subjects alive, in response (CR, CRMRD$^-$, or CRi), and with no new anticancer therapy (except for allo-SCT) will be censored at the last evaluable disease assessment

- Subjects with no evaluable disease assessment at the data cutoff date, who are yet to reach the Week 6 disease assessment, will be censored at the KITE-222 infusion date.

KM estimates and 2-sided 95% CIs will be generated for EFS. Estimates of the proportion of subjects with EFS at 3-month intervals will be provided.

9.9.6. Overall Survival

OS is defined as the time from KITE-222 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

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

9.9.7. 30- and 60-day All-cause Mortality

The mortality rate is calculated by number of deaths, regardless of cause, within 30 or 60 days from the KITE-222 infusion date divided by the total number of subjects included in the safety analysis set. The incidence of 30- and 60-day mortality and exact 2-sided 95% CIs will be generated.

9.9.8. MRD$^-$ Response Rate

The incidence of MRD$^-$ response per the ELN 2017 Classification (as defined in Section 12.5) will be summarized. Corresponding exact 2-sided 95% CIs will be generated.

For subjects achieving CR who have not undergone allo-SCT, MRD$^-$ at 6 months, 12 months and 24 months will also be summarized.

9.10. Safety Analysis

Subject incidence of treatment-emergent adverse events (TEAEs), defined as any AEs with onset on or after the date of KITE-222 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 (PT) and/or system organ class (SOC). CTCAE grade changes in safety laboratory values will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized. Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Time to neutrophil recovery and time to platelet recovery after KITE-222 infusion and before the start of the conditioning therapy for allo-SCT will be summarized with descriptive statistics as follows:

- Time to neutrophil recovery will be calculated as the time from the date of KITE-222 infusion to the first day when neutrophils are 0.5×10^9/L, and as the time from the date of KITE-222 infusion to the first day when neutrophils are 1.0×10^9/L.

- Time to platelet recovery will be calculated as the time from the date of KITE-222 infusion to the first day when platelets are 50×10^9/L, and the time from the date of KITE-222 infusion to the first day platelets are 100×10^9/L.

The percentage of primary graft failure after allo-SCT with the 95% CIs will be summarized.

The incidence of anti-KITE-222 CAR antibodies will be summarized. Tables and/or narratives of deaths through the long-term follow-up period and treatment-related SAEs will be provided.

9.11. Pharmacokinetics Analysis

For each pharmacokinetic time point, the peak, AUC, and time to peak will be tabulated for KITE-222 CAR T cells.

Additional pharmacokinetic analyses may also be performed and details of these analyses will be included in the supplementary SAP.

9.12. Pharmacodynamics Analysis

For each pharmacodynamics time point, the peak, AUC, and time to peak will be tabulated for key analytes (pro-inflammatory and immune-modulating cytokines, chemokines, and effector molecules) in serum over time.

Additional pharmacodynamic analyses may also be performed, and details of these analyses will be included in the supplementary SAP.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Kite or Gilead, or proprietary interests in the IP during the course of the clinical study. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Kite of any change in reportable interests during the study and for 1 year after completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

10.1.2. IRB/IEC Approvals

A copy of the protocol, ICF, and any additional subject or trial information such as subject recruitment materials must be submitted to each sites' respective IRB/IEC for approval. 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 the 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-specific 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.

10.1.3. Informed Consent

Before a subject can participate in this study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, the anticipated benefits, and the potential risks. The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the most current IRB/IEC-approved ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with the institution's 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 reconsented with any updated version of the IRB/IEC-approved ICF if relevant to their participation in the study.

CCI [redacted]

10.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an ID code and any other unique identifier(s) as allowed by local law (such as subject's year of birth) will be recorded on any form or biological sample submitted to Kite or the laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject (refer to specific laboratory instructions for further information). Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Kite, including but not limited to the IB, this protocol, eCRFs, the study drug, and any other study information, remain the sole and exclusive property of Kite during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Kite. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

Per the Federal regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, CRO, IRB/IEC and regulatory agencies to subject's original source documents for the verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which include personal information.

Subject confidentiality must be maintained on all material submitted to the key sponsor contact. The following rules are to be applied:

- Subjects will be identified by a unique ID number
- Subject's year of birth/age at the time of enrollment will be reported according to local laws and regulations

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

10.1.5. Study Files and Retention of Records

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

Source documents are original documents, data, and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries.

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

- Subject content including the ICFs and subject ID lists
- Essential documents for the conduct of this clinical study
- Proof of receipt, experimental treatment flow records, and experimental product-related correspondence

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

The required source data should include sequential notes containing at least the following information for each subject:

- Subject ID
- Documentation that the subject meets the eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support eligibility criteria])
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in the study (including study number/name)
- Study discussed and the date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed

- Results of efficacy parameters, as required by the protocol
- Start and end date (including the dose regimen) of IP, including start and stop times of KITE-222 administration
- Record of all AEs and other safety parameters (the start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including the start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

Traceability records for the product, from procurement through manufacture to the administration of the product, should be kept by each relevant party (eg, the sponsor and the investigator/institution) for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by agreement with the sponsor. Before, during, and after completion or termination of the trial, each party should hold the necessary information available at all times to ensure bidirectional traceability, linking the subject information at the procurement site to the product and the subject information at the clinical trial site to the product, while ensuring the data protection legally required for the subject.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Kite to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

If a subject transfers to another study site, the investigator must notify Kite in advance before assigning the subject's study records to another party or moving them to another location.

10.1.6. Electronic Case Report Forms

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

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will only capture the data required per the protocol SOA. The eligibility criteria and enrollment eCRFs should be completed only after all the data related to the study eligibility have been received. Data entry should be performed in accordance with the eCRF completion guidelines provided by the sponsor.

Subsequent to the data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Kite staff, who routinely review the data for

completeness, correctness, and consistency. The site investigator or site coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). The original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, before any interim time points or database lock (as instructed by Kite), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents.

At the conclusion of the study, Kite will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 10.1.5.

10.1.7. Access to Study Information

The investigator will make available all source documents and other records for this study to Kite's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors. By signing the investigator statement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits, audits, and regulatory authority inspections.

10.1.8. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations as described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce an immediate risk to study subjects, may be made only by Kite. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented approval from the IRB/IEC before modifications can be implemented. Documentation acknowledging the agreement with the protocol amendment from the investigator and approval from the IRB/IEC are to be submitted to the key sponsor contact.

10.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. Kite will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may not communicate study results via oral presentation, scientific publication, or other scholarly media until the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Kite in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

- The investigator will submit to Kite any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before the submission of the publication or presentation.

- No such communication, presentation, or publication will include Kite's confidential information (see Section 10.1.4).

The investigator will comply with Kite's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

10.2.3. Financing and Insurance

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

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Kite will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the ICH E6 (R2) addendum to its guideline for GCP and applicable laws and regulations.

10.3.2. Ethics

Study KT-US-486-0201 will be conducted under a US investigational new drug (IND) application or equivalent and in accordance with recognized international scientific and ethical standards, including but not limited to the ICH guideline for GCP, and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US CFR Title 21, Part 312 [(21CFR312)], and the European Community Directive 2001/20/EC, as well as other local legislation.

10.3.3. Quality Control and Quality Assurance

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

The monitor is responsible for source document verification of eCRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed.

In accordance with ICH GCP and the audit plan, a site may be chosen for a Kite Quality Assurance site audit. A Kite Quality Assurance 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. Investigators will provide the Kite Quality Assurance auditors access to subject records.

Representatives of regulatory authorities may conduct inspections of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Kite medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.4. Study Discontinuation

Both Kite 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 of the trial completion or early termination.

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12. APPENDICES

12.1. Sponsor and Investigator Signature Page

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

STUDY ACKNOWLEDGMENT

A Phase 1 Open-label, Multicenter Study Evaluating the Safety of KITE-222, an Autologous Anti-CLL-1 CAR T-cell Therapy in Subjects with Relapsed/Refractory Acute Myeloid Leukemia

Version: Amendment 4.0, 17 January 2023

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

PPD

Name (Printed)
Kite Medical Monitor

18-Jan-2023

Date

PPD

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 1 year after the study is completed.

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

12.2. Schedule of Assessments

The SOA and procedures to be performed during the treatment and post-treatment follow-up periods are presented in Table 10. The SOAs and procedures to be performed during the follow-up period are presented in Table 11 and Table 12.

Table 10. Schedule of Assessments – Treatment Period and Post-treatment Follow-up Period

Timeframe:	Screening (Days Before Enroll-ment)		Pretreatment Period					Inpatient Hospitalization Period					Post-treatment Follow-up						
			Enrollment/ Leuka-pheresis	CCI		Lympho-depleting Chemo-therapy		Infusion of KITE-222 (D0) and Monitoring					Without Allo-SCT (calculated from D0)					With Allo-SCT	
Procedures	≤14d	≤7d	Within approx. 7 days after eligibility confirmation[A]	CCI		CCI		IP D0	D1 to D13	W2 (±2d)	D15 to D27	W4[C] (±3d)	W5 (±3d)	W6[C] (±3d)	W7 (±3d)	M2[C] (±1w)	M3[C] (±1w)	Allo-SCT: within 1 week before CC	D-1 of Allo-SCT
Demographic data	X			CCI															
Medical history[D]	X																		
Previous cancer treatment history	X																		
Physical examination[E,F]		X				X		X		X		X		X		X	X	X	
Vital signs[F,G]		X	X			X		X	QOD	X	QOD	X		X		X	X	X	
ECOG performance status		X				X		X											
Weight (plus height at screening)		X	X																
Neurologic examination and assessment (ICE score)[H]	X							X	QOD	X		X					X	X	
ECG	X																		
ECHO[I]	X																		
Brain MRI or CT (if MRI is not feasible)[Z]	X																		
Chest imaging (x-ray or CT or MRI scan)		X																	
Lumbar puncture (for CSF)[E,J]	X[J]								X[J]										

Timeframe:	Screening (Days Before Enroll-ment)		Pretreatment Period	CCI	Lympho-depleting Chemo-therapy			Inpatient Hospitalization Period					Post-treatment Follow-up						
			Enrollment/ Leuka-pheresis					Infusion of KITE-222 (D0) and Monitoring					Without Allo-SCT (calculated from D0)					With Allo-SCT	
Procedures	≤14d	≤7d	Within approx. 7 days after eligibility confirmation[A]					IP D0	D1 to D13	W2 (±2d)	D15 to D27	W4[C] (±3d)	W5 (±3d)	W6[C] (±3d)	W7 (±3d)	M2[C] (±1w)	M3[C] (±1w)	Allo-SCT: within 1 week before CC	D-1 of Allo-SCT
Disease assessments																			
BM aspirate[K] and MRD	X									X		X		X			X	X	
BM biopsy[K]	X									X									
Extramedullary disease assessment (only subjects with non-CNS extramedullary disease)[L]	X											X					X	X[L]	
CCI																			
Overall disease assessment	X									X		X		X			X	X	
Local laboratory assessments																			
Chemistry panel (includes CrCl at screening and before lymphodepleting chemotherapy) (serum)[F]		X	X		X			X	X	X	D21 ±2d	X		X		X	X	X	
Coagulation (plasma)[N]		X	X		X			X	X	X	D21 ±2d	X		X		X	X	X	
CBC with differential (blood)[O]		X	X		X			X	X	X	QOD	X	X	X	X	X	X	X	X
CRP, ferritin, LDH[P] (serum)		X			X			X[P]	D1-7[P]	X[P]									
Pregnancy test (serum or urine)[Q]	X[Q]																X[Q]		
Donor chimerism[R]			X																
Serology (EU sites)[S]	X[S]																		

Timeframe:	Screening (Days Before Enroll-ment)		Pretreatment Period	CCI			Inpatient Hospitalization Period					Post-treatment Follow-up						
			Enrollment/ Leuka-pheresis		Lympho-depleting Chemo-therapy		Infusion of KITE-222 (D0) and Monitoring					Without Allo-SCT (calculated from D0)					With Allo-SCT	
Procedures	≤14d	≤7d	Within approx. 7 days after eligibility confirmation[A]				IP D0	D1 to D13	W2 (±2d)	D15 to D27	W4[C] (±3d)	W5 (±3d)	W6[C] (±3d)	W7 (±3d)	M2[C] (±1w)	M3[C] (±1w)	Allo-SCT: within 1 week before CC	D-1 of Allo-SCT
Central laboratory assessments																		
Anti-KITE-222 CAR antibodies (serum)[F,T]			X[A]								X					X	X	
Key analytes, including cytokines (serum)[F,U]			X[A]		X		X	QOD	X	D21 ±2d	X				X			
CCI																		
CBC with differential (blood)[F,O]			X[A]		X		X	D3, D7, D10	X	D21 ±2d	X		X		X	X	X	X
CLL-1 expression (blood)			X[A]		X		X		X		X		X			X	X	
Leukapheresis			X															
CCI																		
Fludarabine/cyclophosphamide					X	X	X											
KITE-222 IV infusion							X											
Subsequent therapy for AML[X]								X										
Concomitant medications[F,Y]	X				X												X[Y]	X[Y]
AEs[F,Y], SAEs[F,Y]	X[Y]		X[Y]		X												X[Y]	X[Y]

Abbreviations: AE, adverse event; allo-SCT, allogenic stem-cell transplant; AML, acute myeloid leukemia; approx., approximately; BM, bone marrow; CAR, chimeric antigen receptor; CBC, complete blood count; CLL-1, C-type lectin-like molecule-1; CC, conditioning chemotherapy; CNS, central nervous system; CrCl, creatinine clearance; CRP, C-reactive protein; CRS, cytokine release syndrome; CSF, cerebral spinal fluid; CT, computed tomography; D, Day of study; d, day; ECG, electrocardiogram; ECHO,

echocardiogram; ECOG, Eastern Cooperative Oncology Group; EU, European Union; HIV, human immunodeficiency virus; ICE, immune-effector cell-associated encephalopathy; ICF, informed consent form; IP, investigational product; IV, intravenous(ly); LDH, lactate dehydrogenase; M, month; MRD, measurable residual disease; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; QOD, every other day; CCI ; SAE, serious adverse event; SOA, schedule of assessments; W, Week of study; w, week.

A. Assessments must be done before the start of leukapheresis.
B. Assessments must be done before the start of the dosing of the lymphodepleting chemotherapy.
C. Week (W) or Month (M) X refers to the end of X weeks or months, respectively, after infusion of KITE-222 (eg, Month 6 = 6 months after infusion).
D. **Medical history**: Medical history will include description of the features of the AML at time of diagnosis (including cytogenetics and molecular classification, prior therapies, and responses). It will also include identification of the donor source for a potential allo-SCT.
E. **Physical examination**: Subjects with new-onset symptoms related to CRS should undergo physical examination at least daily until symptoms resolve to baseline. Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings from the physical examination, will have a brain MRI or CT (if MRI is not feasible) and lumbar puncture for examination of CSF.
F. **Assessments to be performed at disease progression:** If a subject's disease progresses, the following procedures will be completed (refer to Section 7.8.2): Disease assessment (including a BM aspirate and CCI); CCI CCI s); key analytes (including cytokines) (serum), CLL-1 expression (blood), anti-KITE-222 CAR antibodies (serum), AE/SAE reporting; and documentation of concomitant medications.
G. **Vital signs:** Includes blood pressure, heart rate, respiration rate, oxygen saturation, and temperature. In addition to the time points outlined in the SOA, it is recommended that vital signs are monitored during and after study treatment and then routinely per institutional guidelines. Vital signs may be monitored more frequently as clinically indicated.
H. **Neurologic examination and assessment:** A neurologic examination including an ICE cognition assessment, should be done during the screening period and before the KITE-222 infusion on Day 0, then every other day until W2 and again on W4, M3 and within 1 week before the conditioning chemotherapy for allo-SCT. If subject has a change in the baseline neurologic examination and assessment, an evaluation should be performed daily until the symptoms return to baseline status. For new onset of neurologic symptoms, a neurologic examination should be performed at least daily until symptoms resolve to baseline (refer to Section 6.3.8).
I. **ECHO:** An ECHO performed after the subject's last chemotherapy treatment and within the 28 days before signing the ICF may be used to confirm eligibility (if the last chemotherapy regimen is not considered cardiotoxic).
J. **Lumbar puncture:**
   - Opening pressures should be measured with each lumbar puncture when possible and recorded in the subject's site chart.
   - Screening: Subjects with a history of CNS malignancy, leptomeningeal carcinomatosis, or symptoms of CNS malignancy (such as new onset severe headaches, neck stiffness, or any focal neurological findings) will undergo a lumbar puncture at the screening visit for examination of CSF to determine the presence of a CNS malignancy.
   - After infusion: During D1 to W4, a lumbar puncture is recommended for subjects with new onset of clinically significant neurologic toxicities of severity Grade 2 or higher after KITE-222 infusion unless contraindicated. CSF samples obtained after KITE-222 infusion will be submitted to the central laboratory and analyzed for levels of key analytes (including cytokines) and presence of CAR T cells.
K. **BM aspirate/biopsy and MRD:**
   - All BM samples are to be submitted to the central laboratory. Biopsy must also be obtained if the corresponding aspiration results in a dry tap. For each BM aspirate collected, a portion of the aspirate will be submitted to the central laboratory on the day of collection and analyzed for MRD; refer to the central laboratory manual for details.
   - Screening/pretreatment period: Both a BM aspirate and biopsy will be required during the screening period and must be obtained after the most recent anti-cancer therapy. An archived sample from the original diagnosis should be submitted to the central laboratory if possible. This is in addition to the fresh BM sample (aspirate and biopsy) obtained at screening disease assessment. The archived sample may be either a formalin-fixed paraffin-embedded BM biopsy or approximately 20 unstained slides. The archived samples will be submitted to the central laboratory once the study eligibility has been confirmed.
   - Bridging therapy: BM aspirate and biopsy sample must be repeated in subjects receiving bridging therapy. This assessment should occur 1 to 2 days before the initiation of lymphodepleting chemotherapy or as close to the planned date of lymphodepleting chemotherapy as feasible to ensure the subject still meets eligibility criteria for the study based on morphologic disease.

- Inpatient hospitalization period and post-treatment follow-up: BM aspirate and biopsy will be required at Week 2. Please refer to Section 12.4 for additional country-specific requirements. Additionally, BM aspirates are required at Week 4, Week 6, and Month 3; if the BM aspirate is either a dry tap or is hemodiluted, a biopsy must be obtained.
- Allo-SCT: BM aspirate and biopsy (only if dry tap aspirate) must be performed within 1 week before the start of the conditioning chemotherapy for allo-SCT.

L. **Extramedullary Disease Assessment:** Extramedullary disease assessment must be repeated for subjects who received bridging therapy. This assessment should occur 1 to 2 days before the initiation of lymphodepleting chemotherapy or as close to the planned date of lymphodepleting chemotherapy as feasible to ensure the subject still meets eligibility criteria for the study based on morphologic disease. Subjects should undergo extramedullary disease assessment within 1 week before the start of conditioning chemotherapy for allo-SCT, unless obtained within 4 weeks before the start of conditioning chemotherapy.

M. CCI [redacted]

N. **Coagulation** (blood): Includes prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen assessments.

O. **CBC with differential** (blood):

- Local laboratory assessments: Blood should be collected at the time points specified or until disease progression or relapse, whichever occurs first, and sent to the local laboratory for clinical/safety evaluation. CBC with differential including percentage blasts should continue to be sent to the local laboratory daily until the subject's absolute neutrophil count is > 1.0×10^9/L and platelets are > 100×10^9/L while the subject is hospitalized or until they start a conditioning regimen for allo-SCT. After allo-SCT, institutional guidelines will be followed. In addition, a CBC with differential, including blast quantification, is needed within 3 days of any BM sampling. CCI [redacted]
- Central laboratory assessments: With each PBMC submission to the central laboratory, a blood sample for assessment of CBC with differential should be submitted to the central laboratory to allow for more rapid analysis of KITE-222 CAR T-cell levels in the blood. These samples are in addition to samples collected at specified time points and that are sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation.

P. **LDH** (serum): Monitoring of LDH after KITE-222 infusion is recommended only if LDH is elevated at baseline. In addition, LDH should be monitored as clinically indicated.

Q. **Pregnancy test** (serum or urine): After transplantation, routine surveillance testing according to institutional guidelines should be followed. For EU sites, the test is to be completed within the 7 days before leukapheresis, lymphodepleting chemotherapy, and conditioning chemotherapy in case of allo-SCT for females of childbearing potential. Check country-specific requirements in Section 12.4.

R. **Donor chimerism:** For subjects with a prior history of allo-SCT, donor chimerism should be assessed within approximately 7 days after eligibility confirmation (when available per the local laboratory).

S. **Serology** (serum): For EU sites, viral serologic tests (eg, HIV, hepatitis B, hepatitis C, and syphilis) will be carried out per institutional guidelines and EU regulations. Testing may be performed within 30 days before leukapheresis/enrollment and/or on the day of leukapheresis/enrollment.

T. **Anti-KITE-222 CAR antibodies** (serum): Baseline antibody samples are to be collected before the start of leukapheresis.

U. **Key analytes (including cytokines)** (serum) **and KITE-222 CAR T cells** (PBMCs):

- If a subject is readmitted to the hospital with any KITE-222-related AE after the initial hospitalization for KITE-222 infusion, a serum sample for the assessment of the levels of key analytes (including cytokines) and KITE-222 CAR T cells will be collected on the day of hospital readmission and then weekly through, and including, the day of discharge.
- If the subject experiences a Grade 2 or higher KITE-222-related toxicity, such as Grade 2 CRS or neurologic event, 1 additional blood draw for key analytes (including cytokines) and KITE-222 CAR T cells will be taken at the time of the Grade 2 or higher KITE222 related toxicity and upon resolution of the event.
- Serum for assessment of key analytes (including cytokines) and PBMCs for KITE-222 CAR T cells will also be collected at the time of disease progression before starting any subsequent anticancer therapy.

V. CCI [redacted]

W. [redacted] PBMCs will be collected for CCI testing at baseline (before leukapheresis) and at Month 3, Month 6, and Month 12. Thereafter, samples will be held for up to 15 years. Only if a subject's PBMC sample tests positive for CCI at any time point within the first year, samples will continue to be collected and tested annually for up 15 years or as clinically indicated (ie, if there is any reason to suspect CCI). If a secondary malignancy is suspected during the study or follow-up, every effort will be made to

obtain a blood sample (PBMC) and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to start a testing workflow, including tests such as transgene elements, CCI presence of common cancer-drivers/mutations and insertional mutagenesis. Please refer to Section 12.4 for additional country-specific requirements.

X. Subsequent anticancer therapy for AML: In the case of disease progression, subsequent anticancer therapy administered after KITE-222 infusion for a subject's disease will be recorded in the electronic case report forms for all enrolled subjects until one of the following occurs: subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or dies.

Y. **AEs, SAEs, and concomitant medications:** Collection of AEs starts from the commencement of the leukapheresis procedure. Collection of SAEs starts from signing of the screening ICF. AEs/SAEs/concomitant medications should be collected through 3 months after KITE-222 infusion. After the 3-month follow-up period or start of the conditioning regimen for allo-SCT, whichever occurs first, only targeted concomitant therapies, targeted AEs and targeted SAEs will be recorded. This will continue for 24 months after KITE-222 infusion, or until disease progression or relapse, whichever occurs first. Secondary malignancies will be reported through 15 years after the KITE-222 infusion. All AEs and SAEs deemed related to KITE-222 infusion should be recorded and reported regardless of study period (Table 11 and Table 12). In the case of a secondary malignancy, every effort will be made to obtain a blood sample (PBMC) and biopsy sample or the pertinent autopsy of the neoplastic tissue. This will be investigated with a workflow including tests such as transgene elements, CCI presence of common cancer-drivers/mutations, and insertional mutagenesis. Please refer to Section 12.4 for additional EU country-specific guidance.

Z. **Brain MRI scan:** In the case of a prior history of CNS involvement by AML or clinical symptoms suggesting neurological involvement. A CT scan may be performed if the MRI is not feasible.

Table 11. Schedule of Assessments – Follow-up Period Without Allo-SCT[A]

Procedure (see Notes)	Month 6 ± 2 w	Month 9 ± 2 w	Month 12 ± 2 w	Month 15 ± 2 w	Month 18 ± 2 w	Month 24 (see Notes) ± 1 m	Month 36 ± 1 m	Month 48 ± 1 m	Month 60 ± 1 m	Month 72 ± 3 m; Annually Through Year 15	At Disease Progression or Relapse
Physical examination	X	X	X	X	X	X	X	X	X		X
Disease assessments											
Extramedullary disease assessment[B]	X	X	X		X	X	Standard of care				X
Bone marrow aspirate[C]	X	X	X		X	X	Standard of care				X
Bone marrow biopsy[C]											X[C]
Overall disease assessment	X	X	X		X	X	Standard of care				X
Local laboratory tests											
CBC with differential (blood)[D]	X	X	X	X	X	X					X
Central laboratory tests											
CBC with differential (blood)[D]	X	X	X	X	X	X					X
Anti-KITE-222 CAR antibodies (serum)	X	X	X								X
CCI [redacted]	CCI [redacted]										
CLL-1 expression (blood)	X	X	X	X	X	X					X
Key analytes, including cytokines (serum)											X
Targeted AE/SAEs[G]	X										
Targeted concomitant medications[H]	X	X	X	X	X	X					X
All KITE-222-related SAEs and any deaths regardless of causality	X										
Subsequent therapy for AML[J]	X										
Survival status[K]	X										

Notes: After completing at least 24 months of assessments in this study, all subjects who received an infusion of KITE-222 will be transitioned to a separate LTFU study, after providing informed consent, to complete the remainder of the 15-year follow-up period. See abbreviations and footnotes below Table 12.

Table 12. Schedule of Assessments – Follow-up Period After Allo-SCT[A]

Timeframe After Allo-SCT: Procedure (see Notes)	Month 1 ± 3d	Month 3 ± 1 w	Month 6 ± 2 w	Month 9 ± 2 w	Month 12 ± 2 w	Month 15 ± 2 w	Month 18 ± 2 w	Month 24 (see Notes) ± 1 m	Month 36 ± 1 m	Month 48 ± 1 m	Month 60 ± 1 m	Month 72 ± 3 m; Annually Through Year 15	At Relapse
Physical examination	X	X	X	X	X	X	X	X	X	X	X		X
Disease assessments													
Extramedullary disease assessment[B]	X	X	X		X		X	X	Standard of care				X
Bone marrow aspirate[C]	X	X	X		X		X	X	Standard of care				X
Bone marrow biopsy													X
Overall disease assessment	X	X	X		X		X	X	Standard of care				X
Local laboratory assessments													
CBC with differential (blood)[D]	X	X	X	X	X	X	X	X					
Central laboratory assessments													
CBC with differential (blood)[D]	X	X	X		X			X					X
Anti-KITE-222 CAR antibodies (serum)		X	X	X	X								X
CCI													
CLL-1 expression (blood)	X	X	X	X	X	X	X	X					X
Key analytes, including cytokines (serum)													X
Targeted AE/SAEs[G]	X[G]	X											
Targeted concomitant medications[H]	X[H]	X	X	X	X	X	X	X					X
Engraftment assessment[I]	X												
All KITE-222-related SAEs and any deaths regardless of causality	X												
Subsequent therapy for AML[J]	X												
Survival status[K]	X												

Abbreviations: AE, adverse event; allo-SCT, allogenic stem-cell transplant; AML, acute myeloid leukemia; BM, bone marrow; CAR, chimeric antigen receptor; CBC, complete blood count; CLL-1, C-type lectin-like molecule-1; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; d, day; eCRF, electronic case report form; GVHD, graft-versus-host disease; LTFU, long-term follow-up; m, month; PBMC, peripheral blood mononuclear cell; CCI ; SAE, serious adverse event; w, week.

Notes: After completing at least 24 months of assessments in this study, all subjects who received an infusion of KITE-222 will be transitioned to a separate LTFU study, after providing informed consent, to complete the remainder of the 15-year follow-up period.

A. **Table 11:** Month X refers to the end of X months after infusion of KITE-222 (eg, Month 6 = 6 months after infusion).
   Table 12: Month X refers to the end of X months after allo-SCT (eg, Month 6 = 6 months after allo-SCT).
B. **Extramedullary disease imaging:** Extramedullary disease imaging can be stopped after subject is in CR or CRi if they do not proceed to allo-SCT, until relapse.
C. All BM samples are to be submitted to the central laboratory. Biopsy must also be obtained if the corresponding aspiration results in a dry tap or is hemodiluted. CCI
D. **CBC with differential** (blood):
   - Local laboratory assessments: Blood, including quantification of the percentage of blasts, should be collected at the time points specified through Month 24 or until disease progression or relapse, whichever occurs first, and sent to the local laboratory for clinical/safety evaluation.
   - Central laboratory assessments: With each PBMC submission to the central laboratory, a blood sample for assessment of CBC with differential should be submitted to the central laboratory to allow for more rapid analysis of KITE-222 CAR T-cell levels in the blood. These samples are in addition to samples collected at specified time points and that are sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation.
E. CCI
F. CCI : In the follow-up period, samples should be collected at Months 3, 6, and 12. Only if a subject tests positive for CCI at any time point within the first year, samples will continue to be tested yearly for up 15 years or as clinically indicated, ie, if any clinical reason to suspect CCI. If a secondary malignancy is suspected during the study or follow-up, every effort will be made to obtain a blood sample (PBMC) and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to start a testing workflow, including tests such as transgene elements, CCI, presence of common cancer-drivers/mutations and insertional mutagenesis. Please refer to Section 12.4 for additional country-specific requirements.
G. **Targeted AEs and SAEs:** Targeted AEs/SAEs include neurologic, hematologic (only for subjects who do not undergo allo-SCT), primary graft failure (only for subjects who undergo allo-SCT), infections, new occurrence, or aggravation of GVHD, and secondary malignancy events.
   - Subjects who do not undergo allo-SCT (Table 11): Targeted AEs/SAEs should be collected for 24 months after KITE222 infusion or until disease progression or relapse, whichever occurs first. Only reports of secondary malignancies (defined as the development of any new malignancies, except for a relapse of the primary malignancy, occurring after the KITE-222 treatment) will be collected for up to 15 years.
   - Subjects who undergo allo-SCT (Table 12): Targeted AEs/SAEs should be collected after the start of the conditioning regimen for allo-SCT, through 24 months after KITE-222 infusion or until disease progression or relapse, whichever occurs first. Only reports of secondary malignancies (defined as the development of any new malignancies, except for a relapse of the primary malignancy, occurring after the KITE-222 treatment) will be collected for up to 15 years.
   - All AEs and SAEs deemed related to KITE-222 infusion should be recorded and reported regardless of study period.
   - In the case of a secondary malignancy, every effort will be made to obtain a blood sample (PBMC) and biopsy sample or the pertinent autopsy of the neoplastic tissue. This will be investigated with a workflow including tests such as transgene elements, CCI presence of common cancer-drivers/mutations and insertional mutagenesis.
H. **Targeted concomitant medications**:
   - Subjects who do not undergo allo-SCT (Table 11): Concomitant medications should be collected through 3 months after KITE-222 infusion. From Month 3 onwards targeted concomitant medications should be collected for 24 months or until disease progression or relapse, whichever occurs first. Targeted concomitant medications are immunosuppressive drugs, anti-infective drugs, marrow growth factors, tyrosine kinase inhibitors, and vaccinations.
   - Subjects who undergo allo-SCT (Table 12): Concomitant medications should be collected after KITE-222 infusion through 3 months or until the start of the conditioning regimen for allo-SCT, whichever occurs first. Thereafter, targeted concomitant medications should be collected through 24 months after KITE-222 infusion or until

disease progression or relapse, whichever occurs first. Targeted concomitant medications are immunosuppressive drugs, anti-infective drugs, marrow growth factors, tyrosine kinase inhibitors, and vaccinations.

I. **Engraftment:** date of engraftment of neutrophils and platelets will be captured in the eCRF
J. **Subsequent anticancer therapy for AML:** Subsequent anticancer therapy administered after KITE-222 infusion for a subject's disease will be recorded in the eCRFs for all enrolled subjects until one of the following occurs: subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or dies. Subjects may be contacted by telephone to collect information about subsequent therapy for AML.
K. **Survival status:** Subjects may be contacted by telephone to assess their survival status.

12.3. Childbearing Potential and Birth Control

This study will follow the recommendations from the Clinical Trial Facilitation Group (CTFG) {Clinical Trials Facilitation Group (CTFG) 2014}, as described below.

12.3.1. Definition of Childbearing Potential

A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as having no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this study, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

12.3.2. Birth Control Methods That May Be Considered as Highly Effective

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[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Injectable
  - Implantable[2]
- Intrauterine device (IUD)[2]

[1] Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

12.3.3. Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM). A female condom and a male condom should not be used together.

[3] 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.

[4] 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.

12.4. Country-specific Requirements

France

Inclusion and Exclusion Criteria

The inclusion criterion 1) for France must be considered as follows: “For France, r/r de novo or secondary AML as defined by the ELN 2017 Classification {Dohner 2017} excluding acute promyelocytic leukemia and low-risk ELN patients treated with less than 2 lines of therapy (in the dose-escalation part)"

At the discretion of the investigator and in line with exclusion criterion 26): “Any medical or psychiatric condition likely to interfere with assessment of safety or efficacy of study treatment”, the following should be considered:

- Subjects should not have undergone cerebral radiotherapy within 8 weeks prior to KITE-222 administration.
- Subject inclusion in the clinical trial requires validation through a multidisciplinary collective review.

In addition, it is recommended that subjects should undergo a neurological examination by a neurologist prior to inclusion into the trial, in order to better exclude any neurologic involvement and to facilitate subsequent management in the event of an adverse neurologic event.

Bone Marrow Evaluation and Disease Assessment

CCI [redacted]

Conditioning Chemotherapy

Investigators should be aware of AEs potentially caused by the lymphodepleting agents.

Risk – Cytokine Release Syndrome

Hemophagocytic lymphohistiocytosis (HLH) has similar clinical presentation to that of CRS with similar initial therapeutic management. Investigators should be particularly alert to the need to quickly adjust the management of the event in cases of non-response to CRS treatment.

Table 10. Schedule of Assessments

B-hCG pregnancy test (serum or urine) on all females of childbearing potential within 7 days before the initiation of leukapheresis, at Day 0 (end of exposition to fludarabine and cyclophosphamide), Week 4 and Month 2 and within 1 week before the start of the conditioning chemotherapy before allo-SCT serology (HIV, hepatitis B, hepatitis C, and syphilis) (within 30 days before leukapheresis and/or on the day of leukapheresis).

Germany

An MRI scan will be preferred for the imaging requirements in protocol Section 6.3.7, Section 7.3 and Section 7.7.5.

Table 10. Schedule of Assessments

B-hCG pregnancy test (serum or urine) on all females of childbearing potential within 7 days before the initiation of leukapheresis, at Day 0 (end of exposition to fludarabine and cyclophosphamide), Week 4 and Month 2 and within 1 week before the start of the conditioning chemotherapy before allo-SCT serology (HIV, hepatitis B, hepatitis C, and syphilis) (within 30 days before leukapheresis and/or on the day of leukapheresis).

Criteria to Stop or Pause Enrollment

The appropriate regulatory authorities will be notified within the applicable safety reporting timelines if any of these stopping or pausing rules occur. Accrual will be resumed upon the recommendation of the SRT that may also decide the complete discontinuation of enrollment based on review of all relevant data available.

After enrollment and leukapheresis, a subject must not proceed to the lymphodepleting chemotherapy if criteria described in Section 7.6.3.1 are not satisfied. If it is deemed a subject cannot continue to lymphodepleting chemotherapy, reporting of concomitant medications, AEs and SAEs will follow Table 5, Table 7, and Table 8, respectively.

After the lymphodepleting chemotherapy, a subject must not proceed to the infusion of KITE-222 if criteria described in Section 7.7.1 are not satisfied. If it is deemed a subject cannot continue to KITE-222 infusion, reporting of concomitant medications, AEs and SAEs will follow Table 5, Table 7, and Table 8, respectively.

12.5. Response Criteria in AML (Based on European Leukemia Net 2017 Classification)

Disease assessments at the time points specified in Table 10, Table 11, and Table 12 will be performed by the investigator using the local laboratory (peripheral blood, marrow, and if available, measurable residual disease), physical examination, and extramedullary imaging determinations. Assessments will be captured in the eCRF as described in Section 6.4.

The response criteria for r/r AML are based on the ELN 2017 Classification {Dohner 2017} and are presented in Table 13.

If a hematological or molecular relapse is documented, the date of relapse will be captured in the eCRF.

Extramedullary disease assessment is needed if a baseline extramedullary disease exists or if new symptoms are suggestive of relapse as per Section 6.4.4.

Table 13. Response Criteria in AML (Based on ELN 2017 Classification)

Category	Definition	Comment
Response		
CR without measurable (formerly called minimal) residual disease	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used, and sensitivity of the assay should be reported
CR	BM blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/µL); platelet count ≥100 × 10^9/L (100000/µL)	MRD^+ or unknown
CR with incomplete hematologic recovery	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/µL]) or thrombocytopenia (<100 × 10^9/L [100000/µL])	–
Morphologic leukemia-free state	BM blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	The marrow should not merely be “aplastic”; at least 200 cells should be enumerated, or cellularity should be at least 10%
PR	All hematologic criteria of CR; decrease of BM blast percentage to 5% to 25%; and decrease of pretreatment BM blast percentage by at least 50%	–
Stable disease	Absence of $CRMRD^-$, CR, CRi, PR, and MLFS and criteria for PD not met	–
PD	Evidence for an increase in BM blast percentage and/or increase of absolute blast counts in the blood:	–

Category	Definition	Comment
	• > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline or persistent marrow blast percentage of > 70% over at least 3 months without ≥ 100% improvement in ANC to an absolute level (> 0.5×10^9/L [500/μL], and/or platelet count to > 50×10^9/L [50,000/μL] nontransfused) • > 50% increase in peripheral blasts (WBC x % blasts) to > 25×10^9/L (>25,000/μL) (in the absence of differentiation syndrome) • New extramedullary disease	
Relapse		
Hematologic relapse (after a prior assessment with CRMRD$^-$, CR, or CRi)	BM blasts ≥ 5%, reappearance of blasts in the blood, or development of extramedullary disease	–
Molecular relapse (after a prior assessment CRMRD$^-$)	If studied before treatment, re-occurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported

Abbreviations: AML, acute myeloid leukemia; ANC, absolutely neutrophil count; BM, bone marrow; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CRMRD$^-$, complete remission without measurable residual disease; MFC, multiparameter flow cytometry; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; PD, progressive disease; PR, partial remission; RT-PCR, real-time polymerase chain reaction, WBC, white blood cell.
Source: {Dohner 2017}

12.6. Immune Effector Cell-associated Encephalopathy Score

A guide to the immune effector cell-associated encephalopathy score is presented in Table 14.

Table 14. Immune-effector Cell-associated Encephalopathy Score

Task		Score
Orientation:	Orientation to year, month, city, hospital	4 points
Naming:	Ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following commands:	Ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1 point
Writing:	Ability to write a standard sentence (eg, “Our national bird is the bald eagle”)	1 point
Attention:	Ability to count backwards from 100 by 10	1 point

Note: Immune-effector cell-associated encephalopathy score as developed by the American Society for Transplantation and Cellular Therapy consensus grading for cytokine release syndrome and neurologic toxicity associated with immune-effector cells {Lee 2019}.

12.7. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Subject safety monitoring and follow-up:

   a) Subjects may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

      Mitigation plan: For subjects who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the subjects within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

      i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AEs/SAEs.

      ii) Review the current list of concomitant medications and document any new concomitant medications.

      iii) If applicable, confirm electronic/paper diary questionnaires and patient reported outcomes have been completed and transmitted.

   b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, blood draws, imaging, physical exams).

      Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study because of the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible. Central lab kits may be sent to subject's local hospital lab for sample collection. Relevant imaging (eg, PET-CT, CT) can be done at the subject's local hospital and images transferred or sent to the investigative site. Physical exams can be completed by a local physician with results sent to investigative site.

   c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

      Mitigation plan: The site staff will follow their approved informed consent process and remain in compliance with the local ethics committee/institutional review board and national laws and regulations. Remote consent will be allowed if has been approved by the local ethics committee/institutional review board. The consent process will be documented and confirmed by normal consent procedure at the investigative site at the earliest opportunity.

2) Protocol and monitoring compliance:

   a) Protocol deviations may occur in situations where scheduled visits or procedures cannot be conducted as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure at a protocol-specified time point, an unscheduled visit should be conducted as soon as possible when conditions allow so that the required procedure can be performed. The situation should be recorded and explained as a protocol deviation. Any missed subject visits must be reported in the eCRF, if possible, and recorded as deviations to the protocol because of the pandemic, so that they can be appropriately documented and described in the clinical study report. Any remote study visits that are conducted in lieu of clinic visits because of the pandemic will be documented as protocol deviations related to the pandemic.

   b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability, or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure ongoing data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on-site must be tracked centrally and updated on a regular basis.

3) Missing data and data integrity:

   There may be an increased amount of missing data because of subject's missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

   Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

   Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternative methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

   Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of KITE-222 in study subjects remains unchanged.