STATISTICAL ANALYSIS PLAN

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	KITE-222
Protocol:	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
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CONFIDENTIALITY NOTICE

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	analysis data model
AE	adverse event
Allo-SCT	allogeneic stem cell transplantation
AML	acute myeloid leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
BM	bone marrow
CAR	chimeric antigen receptor
CCR	composite complete remission
CLL-1	C-type lectin-like molecule-1
CNS	central nervous system
CR	complete remission
CRF	case report form
CRi	complete remission with incomplete hematologic recovery
$CRMRD^{-}$	complete remission without measurable residual disease
CRS	cytokine release syndrome
CI	confidence interval
CTCAE	common terminology criteria for adverse event
DLI	Donor lymphocyte infusions
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
EFS	event-free survival
ELN	European Leukemia Net
GVHD	graft-versus-host-disease
HMA	hypomethylating agent
ICANS	immune-effector cell-associated neurotoxicity syndrome
ICE	immune-effector cell-associated encephalopathy
KM	Kaplan-Meier
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MLFS	morphologic leukemia-free state
MRD	measurable or minimal residual disease
MRI	magnetic resonance imaging
MST	MedDRA search term
MTD	maximum tolerated dose
OR	overall remission

OS	overall survival
PBMC	peripheral blood mononuclear cell
PR	partial remission
RCL	replication-competent lentivirus
RP2D	recommended phase 2 dose
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDTM	study data tabulation model
SMQ	standardized MedDRA query
SOC	system organ class
SRT	safety review team
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
WHO	world health organization

1. INTRODUCTION

This statistical analysis plan (SAP) sets forth prospectively the details of statistical analyses that are outlined in protocol KT-US-486-0201 entitled "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".

CCI [redacted]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. 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 relapsed or refractory (r/r) acute myeloid leukemia (AML).

2.1.2. 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

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2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoint of this study is to evaluate the incidence of dose limiting toxicity (DLT) in subjects treated with KITE-222.

2.2.2. Secondary Endpoints

The secondary endpoints of this study are to evaluate:

- Incidence of adverse event (AE)
- Clinically significant changes in laboratory parameters
- Time to neutrophil recovery
- Time to platelet recovery

- Composite complete remission (CCR) rate
- Overall remission (OR) rate
- Relapse-free survival (RFS)
- Allogeneic 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 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

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3. STUDY DESIGN

3.1. Overview

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 study consists of dose escalation cohorts and an expansion cohort.

In the dose-escalation part, 3 dose cohorts CCI [redacted] will be assessed to determine the MTD using a 3 + 3 study design. 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.

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.

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, the subject 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.

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.

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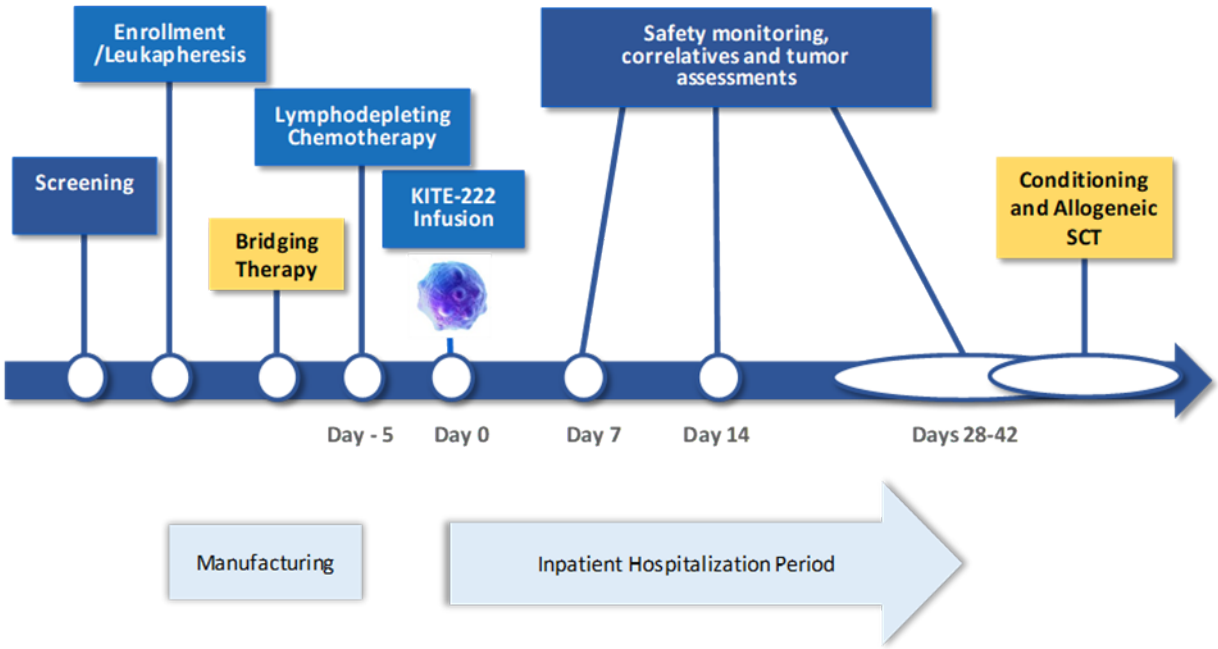
Figure 1. Study Schema



3.2. Hypothesis

There is no formal hypothesis testing in this study. All endpoints will be analyzed by descriptive statistics.

3.3. Sample Size Consideration

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 3.1 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 interval (CIs) of 31% and 69%. Additional assumptions and corresponding 2-sided 95% exact CIs are provided in Table 2.

Table 2. 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

4. COVARIATES

4.1. Baseline Covariates

The following baseline covariates may be used to examine efficacy and/or safety in subgroups or covariate analyses:

- Age (in years) at baseline: < 65, ≥ 65
- Sex
- Race
- ECOG PS
- AML type
- Extramedullary disease assessment
- Risk category per ELN 2017 criteria
- CNS infiltration at diagnosis
- Disseminated intravascular coagulation at diagnosis
- Number of prior chemotherapy lines of therapy
- Prior transplant (yes/no)
- Bridging therapy after leukapheresis and before administration of lymphodepleting chemotherapy (yes/no) and types of bridging
- % of CLL-1+ Blasts in Bone Marrow and peripheral blood

Covariate levels that are sparse may be collapsed for purposes of subgroup analyses. Additional covariates not specified above may be examined for exploration purpose.

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment occurs when a subject is confirmed to be eligible for the study and commences leukapheresis.

Day 0: Day 0 is defined as the day the subject received the KITE-222 infusion. The day before Day 0 will be Day −1. Any days after enrollment and before Day −1 will be sequential and negative integer-valued relative to Day 0. Any days after Day 0 will be sequential and positive integer-valued relative to Day 0.

Baseline: The baseline value is defined as the last non-missing value measured prior to the date of lymphodepleting chemotherapy.

Actual follow-up time: Actual follow-up time among all subjects treated with KITE-222 is calculated as the time from the KITE-222 infusion to the date of death or last date known alive, whichever is later.

Potential follow-up time: Potential follow-up time is defined as the time from the KITE-222 infusion to the data cutoff date for the analysis.

Relapsed/refractory subgroup: Relapsed/refractory subgroups are defined as below for AML and collected in the eligibility page from the eCRF:

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 hypomethylating agent (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

5.2. Safety

5.2.1. Treatment-emergent Adverse Event (TEAE)

TEAE is defined as any AE with onset on or after the infusion of KITE-222.

5.2.2. Time to Onset of a TEAE of Interest

Time to onset of a TEAE of interest is defined as the time from the date of the infusion of KITE-222 until the earliest date of onset of the TEAE in the event class of interest, using the following equation: the start date of the first TEAE in the event class – the date of the infusion of KITE-222 + 1.

5.2.3. Resolution of a TEAE of Interest

A TEAE of interest is considered to be resolved if all TEAEs in the event class of interest are resolved at the time of the analysis data cutoff date. Any TEAE with an end date that is the same as the death date is not considered to be resolved.

5.2.4. Duration of a TEAE of Interest

Duration of a TEAE of interest is defined as the time from the earliest onset date of the TEAE in the event class of interest until the resolution date of the last TEAE in the event class, regardless of any gaps occurring between events (i.e., the resolution date of the last TEAE in the event class – the start date of the first TEAE in the event class + 1). The duration of an AE of interest may be derived only among subjects for whom all events of the class have resolved by the analysis data cutoff date.

5.2.5. TEAEs of Interest

5.2.5.1. Cytokine Release Syndrome

Cytokine release syndrome (CRS) is identified via collection of the syndrome on a CRF specifically designed to collect CRS. Specific symptoms of the CRS are collected on the AE log form and are linked to the CRS syndrome. CRS syndrome severity is graded according to

American Society for Transplantation and Cellular Therapy (ASTCT) grading {Lee 2019}, as shown in Table 3.

Table 3. ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or[b]				
Hypoxia	None	Requiring low flow nasal cannula [c] or blow-by	Requiring high flow nasal cannula [c], face mask, non-rebreather mask, or Venturi mask	Requiring positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome.
Notes: Organ toxicities associated with CRS may be graded according to the Common Terminology Criteria for Adverse Events version 5.0 but they do not influence CRS grading.

a Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or corticosteroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b The CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

c Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

5.2.5.2. Immune effector cell-associated neurotoxicity syndrome

Immune effector cell-associated neurotoxicity syndrome (ICANS) will be assessed by the ASTCT grading {Lee 2019}, as shown in Table 4. (Using immune-effector cell-associated encephalopathy [ICE] scores as determined by Table 5)

Table 4. ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score [a]	7 to 9	3 to 6	0 to 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolved rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviation: ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune-effector cell-associated encephalopathy; ICP, Intracranial Pressure; N/A, not applicable; v, version
Notes: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, and raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.
a A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.
b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE version 5.0, but they do not influence ICANS grading.
d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE version 5.0.

Table 5. Immune Effector Cell-associated Encephalopathy Score

Task	Direction	Score
Orientation	State: year, month, city, hospital	4
Naming	Name: 3 objects	3
Following simple command	Follow: simple command	1
Writing	Ability to write a simple sentence	1
Attention	Count: backwards from 100 by 10’s	1

Abbreviation: ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy.
Notes: Scoring: 10, no impairment; 7-9, Grade 1 ICANS; 3-6, Grade 2 ICANS; 0-2, Grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, Grade 4 ICANS.

5.2.5.3. Infections

Infections will be identified as AEs within the system organ class (SOC) of infections and infestations that occur on or after treatment with KITE-222, in standardized medical dictionary for regulatory activities (MedDRA) query (SMQ) of opportunistic infections (narrow search), and in MedDRA high level group terms (HLGT) that capture events of:

Bacterial infection, encompassing preferred terms within the MedDRA HLGT of

- bacterial infectious disorders
- chlamydial infectious disorders

Viral infection, encompassing preferred terms within the MedDRA HLGT of viral infectious disorders.

Unspecified pathogen infections, encompassing preferred terms within the MedDRA HLGT of infections – pathogen unspecified.

In addition, fungal infections will be identified using HLGT of fungal infectious disorders, and summarized in separate category.

5.2.5.4. Cytopenias (Thrombocytopenia, Neutropenia, or Anemia, Including Aplastic Anemia)

Cytopenias (Neutropenia or Thrombocytopenia or Anemia) will be identified as follows:

- Thrombocytopenia will be identified using the SMQ for haematopoietic thrombocytopenia (narrow search).
- Neutropenia will be identified using the following MedDRA preferred terms: febrile neutropenia, neutropenia, neutrophil count decreased
- Anemia will be identified using the SMQ haematopoietic erythropenia (broad search).

Prolonged cytopenias will be defined by any cytopenia present on or after Day 30 post KITE-222 infusion.

5.2.5.5. Hypogammaglobulinemia

Hypogammaglobulinemia will be identified using an MedDRA search term (MST) search strategy defined by Kite.

5.2.5.6. Secondary Malignancies

AEs coded within the SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps) and deaths due to any reason will be reviewed by the Kite Safety and Pharmacovigilance Team for potential secondary malignancies.

5.2.5.7. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) will be identified as events with MedDRA preferred terms in the SMQ of tumor lysis syndrome. The narrow version of this SMQ will be used.

5.2.5.8. Graft-Versus-Host Disease

New occurrence, or aggravation of graft-versus-host disease (GVHD) will be collected through eCRF. The severity of acute GVHD will be graded per Mount Sinai Acute GVHD International Consortium (MAGIC) criteria {Harris 2016}, and the severity of chronic GVHD will be graded per National Cancer Institute (NIH) score {Jagasia 2015}.

5.2.5.9. Immunogenicity

Immunogenicity will be defined as the development of treatment-emergent anti-KITE-222 antibodies specific to the CAR. The incidence of immunogenicity will be identified for subjects who have developed treatment-emergent anti-KITE-222 CAR antibodies.

5.2.5.10. Replication-competent Lentivirus

Pathogenicity of replication-competent lentivirus (RCL) is a potential risk in human gene therapy products and requires longitudinal testing, before and after infusion of KITE-222. A positive RCL test result is defined by detection of RCL in a blood test.

5.2.5.11. Autoimmune Disorders

Autoimmune disorders will be identified using the SMQ of immune-mediated/autoimmune disorders. The narrow version of this SMQ will be used.

5.2.6. Concomitant Medications of Interest

Concomitant medications are defined as the medications administered to subjects on or after the infusion of KITE-222.

Concomitant medication drug baskets of interest for systemic steroids, vasopressors, nonsteroidal immunosuppressants other than tocilizumab, and intravenous (IV) immunoglobulins are defined by Kite and are documented separately.

5.2.7. Concomitant Procedure

Concomitant procedures are defined as the procedures administered on or after the infusion of KITE-222.

5.3. Efficacy

5.3.1. Composite Complete Remission Rate

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.

MRD− response rate is defined as the proportion of subjects who achieve CRMRD− per the ELN 2017 Classification, as determined by the study investigators.

5.3.2. Overall remission (OR) rate

Overall remission (OR) rate (CR + CRMRD− + CRi + morphologic leukemia-free state [MLFS] + partial remission [PR]) per the ELN 2017 Classification, as determined by the study investigators.

5.3.3. Relapse-free survival (RFS)

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.

5.3.4. Allo-SCT Rate

The allo-SCT rate is defined as the number of subjects who receive allo-SCT after being treated with KITE-222 divided by the total number of subjects included in the safety analysis set.

5.3.5. 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 Appendix 5 from the study protocol.

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

5.3.6. Overall Survival

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.

Additional details on the derivation of OS and the specific data modules that will be used to derive the last date known to be alive are provided in Appendix 3.

5.3.7. 30- and 60-day All-cause Mortality

The mortality rate is calculated by number of deaths, regardless of cause, within 30 and within 60 days from the KITE-222 infusion date divided by the total number of subjects included in the safety analysis set.

6. ANALYSIS SETS

6.1. DLT-evaluable Set

The 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:

- Receive the target dose level for that cohort and are followed for at least 28 days after the infusion of KITE-222; or
- Receive a dose of KITE-222 lower than the target level for that cohort and experience a DLT during the 28-day period after the KITE-222 infusion.

6.2. Full Analysis Set

The full analysis set (FAS) consists of all enrolled subjects. The full analysis set will be used for the summary of subject disposition and the listing of deaths.

6.3. Safety Analysis Set

The safety analysis set is defined as all subjects treated with any dose of KITE-222. This is the primary analysis set for safety analyses.

6.4. Modified Intention to Treat Analysis Set

Modified intention to treat (mITT) analysis 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.

7. SAFETY REVIEW AND EARLY STOPPING GUIDELINES

Formal interim analysis of efficacy is not planned for the early trial stopping purpose.

7.1. Safety Interim Analysis

A Safety Review Team (SRT), consisting of study sponsor representatives and including at least one active study investigator, will be chartered to 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.

8. DATA SCREENING AND ACCEPTANCE

8.1. General Principles

The data collection, management, and processing will follow good clinical practice. The database will be subject to the edit checks outlined in the Data Management Plan and additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analysis and the final database lock. For the safety interim analyses, snapshots may include data that have not passed all data cleaning procedures at the time the data are extracted for snapshot.

8.2. Electronic Transfer and Archiving of Data

The Medidata Rave system will be used to collect the data in this study. Raw data extracted from Medidata Rave will be archived prior to any further processing. Datasets including raw data, study data tabulation model (SDTM) data, and analysis data model (ADaM) data for planned analyses will be archived. Any additional unplanned analyses that occur after the primary analysis and prior to the final analysis will also be archived. Key data external to the clinical study database (see below) will be included in the relevant SDTM and ADaM modules when the external data are available.

Data from the central laboratories (including % of blasts, target (CLL-1) expression in the tumor and Measurable Residual Disease (MRD)), the product manufacture (e.g. total T cells infused, CAR T cell transduction rate, duration of manufacturing time, vector copy number per transduced cells, T cell phenotype), central laboratory assessment of subject blood samples (including CAR T cell levels in the peripheral blood, antibody/immunogenicity assays, serum inflammatory markers, RCL testing) will be generated from contract laboratories and Kite. These data will be transferred to Kite data management and held in a peripheral directory and not built into the clinical trial database. Before any analysis, these external data will be merged with the SDTM and ADaM datasets.

8.3. Handling of Missing and Incomplete Data

8.3.1. Efficacy Data

The method for handling missing efficacy data is described in the definition for each efficacy endpoint. Every effort will be made to obtain complete data for all important data points.

If certain data points are missing after all efforts are taken, the missing data may be imputed. In the event of a partial or missing death date, the algorithm in Appendix 1 will be used. Completely missing death dates or partial missing death dates with only the year reported will not be imputed.

8.3.2. Safety Data

Partial AE start dates will be imputed. If AE start dates are missing or incomplete, the algorithm defined in Appendix 1 will be used.

8.4. Detection of Bias

A listing of subjects with important protocol deviations (IPDs) will be generated. The deviations included in this list will include, but are not limited to, violations of eligibility criteria and use of exclusionary medication during the study. Lack of protocol compliance will be evaluated by summarizing the subject incidence of IPDs. High rates of IPDs may indicate bias.

8.5. Outliers

Descriptive statistics may be used to identify potential outliers in any key variables analyzed. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6. Distributional Characteristics

The Clopper-Pearson (an exact interval) method is used to generate 95% CI for the disease response rate. This method assumes that individual subject responses are independent with binomial distribution. While the Clopper-Pearson interval provides adequate coverage probability, it is commonly wider than necessary {Brown 2002}, leading to overly conservative estimates of the lower bound of response rate.

8.7. Validation and Configuration Management

All programs to create the SDTM and ADaM datasets, and tables, listings and figures (TLFs) of analyses and summaries will be validated and maintained according to Standard Operating Procedures to Cell Therapy Studies. The software and version used to generate analyses will be indicated in the archived documentation.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

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.

9.2. Subject Accountability

Summary statistics will be provided for the following:

- The number of subjects in each analysis set
- The number of subjects screened
- The number of subjects enrolled/leukapheresed
- The number of subjects treated with bridging therapy
- The number of subjects treated with lymphodepleting chemotherapy
- The number of subjects treated with KITE-222
- The number of subjects received subsequent allo-SCT
- Summaries of actual and potential follow-up time
- The number of subjects enrolled and treated by site

The reasons for discontinuing treatment and discontinuing study will be summarized.

9.3. Important Protocol Deviations

The clinical study team will define IPD categories and review all potential IPDs. The list of subjects with important protocol deviations will be identified and documented before the database snapshot for the primary efficacy analysis is performed. IPDs will be categorized by deviation type (e.g., study eligibility and use of excluded medication). The subject incidence of IPDs will be summarized overall and by deviation category.

9.4. Demographic and Baseline Characteristics

Summary statistics and frequencies for the demographic and baseline characteristics will be tabulated:

- Age (in years) at baseline and by category (< 65, ≥ 65)
- Sex
- Ethnicity and race
- Weight at leukapheresis
- ECOG performance status at baseline
- Immune Effector Cell-Associated (ICE) score at baseline
- Number of prior chemotherapy lines of treatment and best overall response to the first and to the last prior regimen
- AML type and specification of secondary AML type
- Duration of diagnosis
- Risk category per ELN 2017 criteria
- Genetic abnormality
- WHO classification of AML {Heuser 2020}
- CNS infiltration at diagnosis
- Disseminated intravascular coagulation at diagnosis
- Prior allo-SCT and best overall response corresponding to the allo-SCT.
- The percentage of donor chimerism and DLI treatment (Yes/No) for subjects who have received a prior allo-SCT
- Prior radiotherapy and body site
- Relapsed/refractory subgroup
- Baseline hematological status: absolute white blood cells count, absolute neutrophil count, absolute lymphocyte count, percentage of myeloblasts in peripheral blood, percentage of myeloblasts in marrow.
- % of CLL-1+ Blasts in Bone Marrow and peripheral blood at baseline

9.5. Safety Analyses

Safety analyses will be conducted using the safety analysis set. The primary analysis of safety data will summarize TEAEs, death, and laboratory test results with onset on or after the KITE-222 infusion date and before allo-SCT (if applicable).

AEs will be coded according to the latest version of MedDRA at the time of each analysis. The version of MedDRA may vary over time as the current version in use is updated. The severity of AEs will be graded using the NCI CTCAE version 5.0. The severity of CRS and ICANS events will be graded according to the ASTCT consensus grading {Lee 2019}, and individual symptoms associated with CRS and ICANS will be graded per the NCI CTCAE version 5.0. The severity of acute GVHD will be graded by the MAGIC criteria {Harris 2016} and the severity of chronic GVHD will be graded by the NIH 2014 criteria {Jagasia 2015}.

Fatal AEs that are attributed to deaths associated with disease progression or relapse may be included in the death summary with a primary death reason of "Progressive Disease" regardless of the coded preferred term.

Subjects enrolled, but not dosed with KITE-222, will be followed for AEs for 30 days after the last study-specific procedure, or until initiation of a new anticancer therapy, whichever occurs first. AEs reported for these subjects will be archived in the study database and available in SDTM and ADaM datasets, but will not be tabulated in AE summaries.

Safety summaries will be presented by dose-level cohorts.

9.5.1. Exposure to Study Treatment

Summary statistics and subject listings will be provided for the following:

- Total body surface area-adjusted dose of cyclophosphamide and fludarabine administered as lymphodepleting chemotherapy
- Total CAR T cells in the KITE-222 infusion
- Total T cells in the KITE-222 infusion
- Transduction rate (%)
- Percentages of CD4 and CD8 T cells
- Percentages of T-cell phenotypes
- Interferon-gamma (IFN-γ) by Co-culture

9.5.2. AEs

The subject incidence of the following TEAEs will be tabulated:

- Summary of AEs (including categories such as any, serious, worst severity, AE of interest, treatment-related AE)
- All AEs (by SOC and preferred term)
- All SAEs (by SOC and preferred term)
- All KITE-222-related AEs (by SOC and preferred term)
- All KITE-222-related SAEs (by SOC and preferred term)
- All Grade 3 or higher AEs (by SOC and preferred term)
- All Grade 3 or higher KITE-222-related AEs (by SOC and preferred term)
- Fatal AEs
- AEs of interest

The incidence of neutropenia overlapping with fever will be summarized, and fever group term includes MedDRA preferred terms of pyrexia and hyperthermia.

Summary statistics for the study day of onset, the study day of resolution, and the duration of AEs of interest will be provided. The subject incidence summary of deaths by time periods and a subject listing of deaths will be provided. The primary reasons for death will also be summarized.

Time to neutrophil recovery and time to platelet recovery after KITE-222 infusion and before the start of the conditioning therapy for subsequent 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. A graph plot will be provided, with the horizontal axis representing the follow-up time from the time of baseline and on the vertical axis the absolute neutrophil count. The time of the subsequent allo-SCT will be marked with a vertical line.
- 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. A graph plot will be provided, with the horizontal axis representing the follow-up time from the time of baseline and on the vertical axis the absolute platelet count. The time of the subsequent allo-SCT will be marked with a vertical line.

For patients who receive a subsequent allo-SCT after KITE-222, the following descriptive statistics will be presented:

- The percentage of primary graft failure after allo-SCT with the 95% CIs will be summarized. Primary graft failure is collected from eCRF and defined as no evidence of engraftment or hematological recovery of donor cells within the first month after transplant, without evidence of disease relapse.

- The time to engraftment of neutrophils and platelets will be calculated from the date of the subsequent allo-SCT to the first day of engraftment of neutrophils and platelets. Engraftment is defined as the first of 3 consecutive days with an absolute neutrophil count higher than 0.5×10^9/L, and sustained $>20 \times 10^9$/L platelets, free of transfusion requirements.

The incidence of anti-KITE-222 CAR antibodies will be summarized.

Subgroup analyses of AEs may be generated for selected covariates from the list presented in Section 4.1.

9.5.3. Concomitant Medications and Procedures

The incidences of concomitant medications and procedures used to manage AEs will be tabulated. The subject incidence of concomitant medications will be summarized by medication category and World Health Organization (WHO) Drug coded term. The duration and indication of concomitant medications of interest (eg, systemic steroids, tocilizumab, vasopressors, nonsteroidal immunosuppressants other than tocilizumab, and IV immunoglobulins) may be summarized.

9.5.4. Laboratory Test Results

Laboratory test results will be graded according to the NCI CTCAE version 5.0. The incidence of worst grade laboratory abnormalities post-baseline by grade for all analytes will be summarized. Additional summaries for the shift from baseline to the worst laboratory abnormality grade on or after the KITE-222 infusion may also be generated.

9.5.5. Vital Signs and Physical Examinations

Vital sign and physical examination data will be summarized at selected time points by descriptive statistics. Subject listings may also be provided.

9.6. Efficacy Analyses

Efficacy analyses will be conducted on the mITT analysis set, and the investigator assessment of disease status per the ELN 2017 Classification (Appendix 5 in the study protocol) will be used for disease response related analyses. Sensitivity analysis using FAS may also be provided for key efficacy analyses.

A waterfall plot will be provided representing the percentage change in marrow myeloblasts from baseline to the assessment on Week 4 in the mITT set.

Three separate line plots with median, lower quartile (Q1) and upper quartile (Q3) will be provided for the percentage of myeloblasts in the marrow, the percentage of myelocytes in the marrow, and the percentage of metamyelocytes in the marrow using the mITT analysis set, with the x-axis representing the follow-up time from the baseline. For the subjects received post allo-SCT, the follow-up time will be up to the conditioning chemo for the allo-SCT.

A listing of the extramedullary disease assessment evaluation with be provided sorted by Dose Level, patient identification and time.

A listing of the text reports of the marrow disease assessments will be provided sorted by Dose Level, patient identification and time.

9.6.1. Composite Complete Remission Rate

The incidence of CCR 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 non-responders for the CCR rate evaluation.

Additional analysis of CCR using the FAS and by dose level cohorts will be provided.

CCI [redacted].

9.6.2. Overall Remission Rate

The incidence of the OR rate 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 non-responders for the OR rate evaluation.

9.6.3. RFS

Kaplan-Meier (KM) 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.

The number of subjects censored and the reasons for censoring will be summarized.

9.6.4. 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.

9.6.5. EFS

KM estimates and 2-sided 95% CIs will be generated for EFS. Estimates of the proportion of subjects with EFS at 3-month intervals from KITE222 infusion will be provided.

The number of subjects censored and the reasons for censoring will be summarized.

9.6.6. OS

KM estimates and 2-sided 95% CIs will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals from KITE222 infusion will be provided.

A swim lane plot will be provided, with the horizontal axis representing the follow-up time from the time of the KITE-222 infusion and each lane representing a subject. On each lane, endpoints of interests such as disease responses, subsequent allo-SCT, first subsequent AML therapy (apart from allo-SCT), and death will be marked at the time when they occur. The swim lane will be sorted by dose level and longest survival time within each level.

9.6.7. 30- and 60-day All-cause Mortality

The incidence of 30- and 60-day mortality and exact 2-sided 95% CIs will be generated.

9.7. Pharmacokinetics and Pharmacodynamics

Details of pharmacokinetic (PK) and pharmacodynamic (PD) analyses will be described in a separate Translational SAP.

9.8. Study Key Metrics

Summary statistics will be provided for the following durations:

- Days from leukapheresis to commencement of lymphodepleting chemotherapy
- Days from leukapheresis to the KITE-222 product release
- Days from leukapheresis to delivery of KITE-222 at the study site
- Days from leukapheresis to administration of KITE-222
- Days from lymphodepleting chemotherapy to administration of KITE-222
- Days from the administration of KITE-222 to the day of receiving subsequent allo-SCT
- Duration of hospitalization for the KITE-222 infusion
- Number and duration of ICU hospitalizations in the first month from KITE-222 infusion

Successful manufacturing rate of KITE-222 will be calculated as number of KITE-222 product release divided by the total number of subjects included in the FAS at each dose level.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

None.

11. REFERENCES

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Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625-38.

12. APPENDICES

Appendix 1. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates

The following dates will be imputed using the algorithm in Table 1:

- Adverse event (AE) start dates
- Concomitant medication start dates

Table 6. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< Day 0	≥ Day 0	< Day 0 *yyyymm*	≥ Day 0 *yyyymm*	< Day 0 *yyyy*	≥ Day 0 *yyyy*	
Partial *yyyymm*	= Day 0 *yyyymm*	2	1	2	1	n/a	1	1
	≠ day 0 *yyyymm*		2		2	2	2	2
Partial *yyyy*	= Day 0 *yyyy*	3	1	3	1	n/a	1	1
	≠ Day 0 *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

Abbreviation: n/a, not applicable.
Notes: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.
1 = impute the date of Day 0.
2 = impute the first of the month.
3 = impute January 1 of the year.
4 = impute January 1 of the stop year.

Imputation rules for partial or missing death dates:

- If death year and month are available, but day is missing:
  - If mmyyyy for the last date known to be alive = mmyyyy for death date, set death date to the day after the last date known to be alive.
  - If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.
  - If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.
- If both month and day are missing for death date or a death date is completely missing, do not impute, and censor the subject survival time per rules in Appendix 3.

Imputation rules for original date of diagnosis:

1) 1. If year and month are available but day is missing, then impute the first day of the month.
2) 2. If year is available but month and day are missing, then impute January 1 of the year.

Appendix 2. Derivation of Time to Event Endpoints

The derivations of RFS, EFS, and OS are provided below.

RFS

Table 7. RFS Analysis

Circumstance by Data Cutoff for Analysis	Event/Censored	Date of Event / Censoring
Relapse	Event	First relapse date
Death due to any reason	Event	Death date
Receive SCT before relapse	Censored	Last evaluable disease assessment date prior to data cutoff
New anti-cancer therapy (excluding SCT) started before relapse	Censored	Last evaluable disease assessment date prior to the first new therapy (excluding SCT)
Withdrawal of consent or lost to follow-up without relapse	Censored	Last evaluable disease assessment date prior to data cutoff date
Remain in response without new anti-cancer therapy (including SCT) by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date

Abbreviations: SCT, stem cell transplant.
Note: Time to event = Event / Censoring date - First response date + 1.

EFS

Table 8. EFS Analysis

Circumstance by Data Cutoff for Analysis	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death due to any reason	Event	Death date
Relapse	Event	First relapse date
refractory disease*	Event	Disease assessment date at Week6
New anti-cancer therapy (excluding SCT) started before PD, relapse or refractory disease	Censored	Last evaluable disease assessment date prior to the first new therapy (excluding SCT)
Withdrawal of consent or lost to follow-up before PD, relapse or refractory disease	Censored	Last evaluable disease assessment date prior to data cutoff date
Remain in response** without new anti-cancer therapy (including SCT) by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date
Disease response yet to be assessed and not reach to Week 6 disease assessment	Censored	KITE-222 infusion date

Abbreviations: PFS, progression-free survival; SCT, stem cell transplant. PD, progressive disease.
* defined as the subject not experiencing CR, CRMRD−, or CRi by the Week 6 disease assessment.
**defined as alive, in response (CR, CRMRD−, or CRi)
Note: Time to event = Event / Censoring date - First infusion date + 1

Appendix 3. Censoring Criterion for OS and Derivation of Last Date Known to Be Alive

The scenarios describing when the event occurs or the subject is censored for the analysis of OS are presented in Table 9.

Table 9. OS Analysis

Circumstance	Event/Censored	Date of Event/Censoring
Death before data cutoff date for analysis	Event	Death date
Death after data cutoff date for analysis	Censored	Data cutoff date
Known to be alive after data cutoff date for analysis	Censored	Data cutoff date
Alive up through the discontinuation of study, or data cutoff date and no further information available afterwards	Censored	Last date known to be alive date up through the date of discontinuation of study, or data cutoff date, whichever is earlier

Note: Time to event = Event / Censoring date - First infusion date + 1

Last Date Known to be Alive

The last date known to be alive with be derived by obtaining the maximum complete date among the following data modules:

- Leukapheresis dates
- Bridging therapy administration dates
- Lymphodepleting chemo administration dates
- KITE-222 infusion dates
- Start date of AE and end date of AE if the date is available
- Disease response assessment date
- The last date the lab data or vital sign measured
- The last date the concomitant medication received
- The last date of subsequent therapy for AML
- Long-term follow-up subject status date where status = alive
- End of treatment disposition where status is not equal to death, lost to follow-up
- End of study date where end of study reason is not equal to death, lost to follow-up

- Date of subsequent allo-SCT
- Date of engraftment after allo-SCT

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	14-Jul-2022 13:40:25
PPD	Global Patient Safety eSigned	14-Jul-2022 17:49:21
PPD	Clinical Research eSigned	14-Jul-2022 18:12:01
PPD	Clinical Pharmacology eSigned	15-Jul-2022 11:54:17