STATISTICAL ANALYSIS PLAN

Protocol Title	A Phase 1 Dose-Escalation Study of LAM-003 in Patients with Acute Myeloid Leukemia
Investigational Product	LAM-003
Protocol Number/Version	LAM-003-HEM-CLN02, Version 8 (4 November 2019)
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DOCUMENT HISTORY

Protocol Title: A Phase 1 Dose-Escalation Study of LAM-003 in Patients with Acute Myeloid Leukemia

Protocol Number LAM-003-HEM-CLN02

SAP Version Number	Version Date	Description of Changes
1.0	21 August 2020	• Not applicable

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AMA	American Medical Association
AML	acute myeloid leukemia
ANC	Absolute neutrophil count
ATC	Anatomical-Therapeutic-Chemical (drug coding system)
AUC	area under curve
BMI	body mass index
BOR	best overall response
C1/F	apparent clearance
CI	confidence interval
C_{max}	maximum concentration
CR	complete remission
CRc	composite complete remission
CRi	complete remission with incomplete blood count recovery
CR_{MRD-}	complete remission without minimal residual disease
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of remission
DRP	disease recurrence or progression
ECG	electrocardiogram, electrocardiographic
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
FAS	full analysis set
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase-3
HSP90	heat shock protein-90
ICH	International Conference on Harmonization
ITD	internal tandem duplications
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	nonevaluable
NGS	next-generation sequencing
NK	natural killer (cell)
OR	objective remission
ORR	overall remission rate
OS	overall survival
PCR	polymerase chain reaction
PD-L1	programmed death ligand 1
PR	partial remission
PT	preferred term
QD	once per day
QTc	cardiac QT interval corrected for heart rate
QTcF	cardiac QT interval corrected for heart rate using Fridericia formula
RDR	recommended dosing regimen
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System (software)
SOC	(MedDRA) System Organ Class
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
TF	treatment failure
t_{max}	time of maximum concentration
TTR	time to remission
V_d	volume of distribution
WHODRUG	World Health Organization Drug Dictionary
λ_z	terminal elimination rate constant

1. INTRODUCTION

1.1. Purpose and Scope of this Document

As per International Conference on Harmonization (ICH) E9 guidelines [FDA 1998] the purpose of this statistical analysis plan (SAP) is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol document for Study LAM-003-HEM-CLN02 and to include detailed procedures for executing the statistical analysis of the study endpoints and other collected data.

This SAP describes only the statistical summaries that are to be performed by Ce3, Inc. Statistical summaries to be provided by AI Therapeutics, Inc., including summaries of pharmacokinetic and pharmacodynamic data, are not described in this document.

This SAP is based on Version 8.0 of the clinical trial protocol (dated 4 November 2019) and on the version of the electronic case report forms (eCRFs) current as of the date of this version of the SAP. If there are additional amendments to the protocol or eCRFs, this SAP will be updated, as appropriate.

The results of the analyses described in this SAP will be included in the clinical study report (CSR). Any post-hoc or unplanned analyses performed to provide results for inclusion in publications or other reports but not identified in this prospective SAP will be identified in the relevant documents.

Activities related to the development, approval, and maintenance of the SAP, along with study analysis and reporting will be the responsibility of the assigned study team members. After completion of the cohort review and evaluation and sign-off of the final CSR, all applicable datasets, outputs, programs, and specification documents will be transferred to the study sponsor for archiving.

1.2. Study Design

Based on the knowledge regarding the role of heat shock protein-90 (HSP90) in acute myeloid leukemia (AML), AI Therapeutics, Inc has developed LAM-003 as a clinical HSP90 inhibitor for patients with relapsed or refractory AML. The goal of development has been to offer a novel treatment approach that can circumvent drug resistance in patients who have experienced failure of other therapies. Ultimately, it is hoped that LAM-003 administered alone or in combination can supplement or complement current treatment methods.

This clinical trial is a Phase 1 study evaluating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of LAM-003 across a range of LAM-003 dose levels when administered to subjects with previously treated relapsed or refractory AML. Subjects self-administer oral LAM-003 once per day (QD) continuously in repeated 28-day cycles. Cohorts of 3 to 6 subjects are sequentially enrolled at progressively higher starting dose levels of LAM-003 using a standard 3 + 3 design, as indicated in Table 1. The initial cohort of subjects is prescribed LAM-003 at Dose Level 1 (200 mg). Dose Levels -1 (100 mg) and -2 (50 mg) are provided to permit dose decrements if a subject experiences a treatment-emergent adverse event (TEAE) requiring dose modifications to levels below Dose Level 1.

Table 1: LAM-003 Starting Dose Levels

Dose Level	LAM-003 Dosing Regimen	Dose Change Relative to Prior Dose
-2	50 QD	0.50
-1	100 QD	0.50
1 (initial dose level)	200 QD	Not applicable
2	300 QD	1.50
3	450 QD	1.50
4	600 QD	1.33
5	750 QD	1.25

Abbreviation: QD=once per day

Individual subjects who are tolerating the current dose level with no toxicities of Grade ≥ 2 have had the LAM-003 dose escalated to the next higher dose level after ≥ 1 cycle of therapy. In such subjects, successive adjustments to progressively higher dose levels are allowed at intervals of ≥ 4 weeks with the caveat that the escalated dose cannot exceed 750 mg QD (highest plan dose level) or the established maximum tolerated dose (MTD) (if lower).

Based on the pattern of dose-limiting toxicities (DLTs) observed in Cycle 1, escalations proceed to define the MTD and a recommended dosing regimen (RDR) that could be at the MTD or a lower dose within the overall tolerable dose range.

1.3. Study Objectives

1.3.1. Primary Objective

- To determine the MTD and/or RDR of LAM-003

1.3.2. Secondary Objectives

- To characterize the drug administration, safety, and supportive care profiles of LAM-003
- To evaluate the pharmacokinetic profile of LAM-003
- To characterize the onset, magnitude, and duration of antitumor activity and to assess survival in subjects with AML receiving LAM-003

1.3.3. Exploratory Objectives

- To assess the effects of LAM-003 on pharmacodynamic markers relating to drug mechanism, disease, and immune status
- To explore associations between baseline AML characteristics and outcomes in subjects administered LAM-003

1.4. Study Endpoints

1.4.1. Primary Endpoints

- MTD and/or RDR within the tested LAM-003 dose range

1.4.2. Secondary Endpoints

1.4.2.1. Drug Administration, Safety, and Supportive Care Profiles

- LAM-003 drug administration as assessed by prescribing records and subject compliance records
- Type, frequency, severity, timing of onset, duration, and relationship to study drug of any TEAEs; laboratory abnormalities; vital sign/oxygen saturation abnormalities; adverse electrocardiogram (ECG) findings; DLTs; serious adverse events (SAEs); adverse events of special interest (AESIs); or adverse events (AEs) leading to interruption, modification, or discontinuation of study treatment (referencing the Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03, for grading of the severity of AEs and laboratory abnormalities) [NCI 2010].
- Type, frequency, and timing of use of supportive care and other concomitant medications

1.4.2.2. Pharmacokinetics

- LAM-003 and LAM-003A plasma concentrations (as measured using a validated bioanalytical assay)
- Derived LAM-003 and LAM-003A pharmacokinetic parameters (including area under the concentration-time curve [AUC], maximum concentration [C_{max}], time of maximum concentration [t_{max}], volume of distribution [V_d], half-life [$t_{1/2}$], terminal elimination rate constant [λ_z], and apparent clearance [Cl/F]) (as determined using noncompartmental methods)

1.4.2.3. Antitumor Activity and Survival

Efficacy will be evaluated using standard response and progression criteria as adapted for use in the context of protocol therapy for relapsed or refractory AML. Efficacy endpoints will include:

- Complete remission without minimal residual disease (CR_{MRD-}), defined as complete remission (see definition below) with no evidence of AML by flow cytometry
- Complete remission (CR), defined as < 5% bone marrow blasts; no blasts in the peripheral blood; no blasts with Auer rods; no extramedullary disease; and peripheral blood meeting both of the following criteria: Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L
- Complete remission with incomplete count recovery (CRi), defined as < 5% bone marrow blasts; no blasts in the peripheral blood; no blasts with Auer rods; no extramedullary disease; but with peripheral blood meeting either of the following criteria; ANC $< 1.0 \times 10^9$/L or platelet count $< 100 \times 10^9$/L

- Composite complete remission (CRc), defined as CR_{MRD-}, CR, or Cri
- Partial remission (PR), defined as leukemia disease status meeting all of the following requirements: a ≥ 50% decrease in bone marrow blasts to 5% to 25% or < 5% bone marrow blasts but with Auer rods present; no blasts in the peripheral blood; no new or worsening extramedullary disease; and peripheral blood meeting both of the following criteria: ANC ≥ 1.0×10^9/L and platelet count ≥ 100×10^9/L
- Overall remission (OR), defined as achievement of any of CR, CRi, or PR
- Time to remission (TTR), defined as the interval from the start of study therapy to the first documentation of an objective remission
- Duration of remission (DOR), defined as the interval from the first documentation of objective remission to the earliest of the first documentation of disease relapse, disease progression, or death from any cause
- Event-free survival (EFS), defined as the interval from the start of study therapy to the earliest of the first documentation of disease relapse, disease progression, treatment failure, or death from any cause
- Overall survival (OS), defined as the interval from the start of study therapy to death from any cause

1.4.3. Exploratory Endpoints

1.4.3.1. Pharmacodynamics

- Changes in FMS-like tyrosine kinase-3 (FLT3) and HSP (eg, HSP90, HSP70) protein expression and activation of downstream pathway components in AML blasts (as measured using flow cytometry and/or protein immunoblotting)
- Changes in HSP gene expression in AML blasts (as measured using quantitative polymerase chain reaction [PCR])
- Changes in plasma FLT3 ligand concentration (as measured using an immunoassay)
- Changes in programmed death ligand 1 (PD-L1) expression in AML blasts (as measured using flow cytometry)
- Changes in the numbers, cell surface markers, and function of circulating B-cell, T-cell, natural killer (NK) cell, monocyte, and other immune subsets (as measured using flow cytometry)

1.4.3.2. Biomarkers

- Baseline AML blast FLT3 mutation type and FLT3 mutation-to-wild-type allele ratio (as evaluated using the LeukoStrat® CDx FLT3 mutation assay)
- Baseline mutational profile in AML blasts (with germ-line control in saliva) (as assessed with next-generation sequencing [NGS])

1.5. Sample Size Justification

Cohort sample sizes for this study are not based on a specific statistical hypothesis but on experience in the conduct of similar types of Phase 1 dose-ranging studies in subjects with cancer. The total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated.

Cohort sizes of 3 to 6 subjects allow evaluation of regimen safety using a standard method to determine MTD (ie, the highest tested dose level at which ≥ 6 subjects have been treated and which is associated with a DLT in ≤ 17% of subjects during the first cycle of therapy). Based on the planned 3 + 3 dose-escalation scheme, Table 2 shows the probability of escalating to the next dose level based on the true rate of DLT at the current dose level.

Table 2: Statistical Basis for 3 + 3 Dose-Escalation Paradigm

True Incidence of DLT	Probability of Escalating
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

Abbreviation: DLT=dose-limiting toxicity

Thus, if the true underlying proportion of DLT is low (eg, ≤ 10% at the current dose level, there is a high probability (≥ 0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (eg, ≥ 60%) at the current dose level, there is a low probability (≤ 0.08) of escalation to the next dose level.

1.6. Timing of Analyses

1.6.1. Interim Analyses

No formal interim analyses are planned. As described in Section 2.2 of the study protocol, conference calls among the members of the safety review committee will be conducted periodically to discuss study progress, exchange study information, review safety events, determine whether additional dose levels should be evaluated, and discuss potential amendments to the protocol. It is expected that these discussions will be scheduled at intervals of ~2 to 4 weeks unless accrual to the study and decisions regarding study conduct or transitions between the dosing cohorts indicate the need for an alternative schedule of reviews. As needed for scientific or business reasons, AI Therapeutics, Inc. may collate and summarize available study results during conduct of the study.

1.6.2. Final Analyses

Final study reporting is expected to occur after all subjects have discontinued study treatment or ≥ 48 weeks after accrual of the final subjects (whichever occurs earlier).

1.6.3. Follow-up Analysis

After the final analyses, additional supplemental analyses may be performed to assess long-term outcomes and to satisfy regulatory requirements.

2. ANALYSIS CONVENTIONS

2.1. Analysis Sets

The analysis of clinical data will focus on the following analysis sets.

2.1.1. Full Analysis Set

The full analysis set includes all subjects who receive ≥ 1 dose of study drug. This analysis set will be used in the analyses of subject characteristics, study drug administration and compliance, safety, OR, CRc, CR_{MRD-}, CR, CRi, PR, EFS, and OS.

2.1.2. Responding Analysis Set

The responding analysis set includes subjects in the full analysis set who have measurable disease, who can be evaluated for tumor response with both baseline and on-study tumor evaluations, and who achieve a CR_{MRD-}, CR, CRi, or PR. This analysis set will be used in the analyses of TTR and DOR.

2.1.3. Evaluable Analysis Sets

The evaluable analysis sets include subjects in the full analysis set who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest. These analysis sets will be used in the analyses of pharmacokinetic, pharmacodynamic, and biomarker parameters.

2.2. Data Handling Conventions

Analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC, USA).

The clinical database will be locked prior to the initiation of the statistical analyses. A database lock is defined as a stable database that can be analyzed and reported. Changes to a locked database must be authorized in writing by the study sponsor and Ce3 according to Ce3 standard operating procedures.

The data conventions include the following:

- Data will be described and summarized by starting dose level.
- Summary tables for continuous variables will contain the following statistics: N (number of subjects in the population); n (number of subjects with data); mean; standard deviation; median; minimum; and maximum. Selected statistics may also include a 2-sided 95% normal approximation confidence intervals (CIs) on the mean.
- Summary tables for categorical variables will include: N (number of subjects in the denominator); n (number of subjects in the numerator); and percent. Selected statistics also may include 2-sided 95% CIs for the percent.

- The baseline value for a given parameter is the last value prior to the first dose. A value is post-baseline if it is obtained after the first dose. A value is considered to be post dose on a given cycle day if it is obtained after the dose is administered on that day.
- Data from all study centers will be pooled for all analyses.
- Unless otherwise specified, statistical testing will be 2-sided at a nominal 0.05 level of significance.
- Study day is defined as calendar date – date of first treatment + 1 if the calendar date is on or after the date of first treatment, and calendar date – date of first treatment if the calendar date is before the date of first treatment
- Measurements from unscheduled visits will be included in listings but not in summary tables.
- Missing data conventions for individual endpoints are described in the SAP section for the endpoint.
- Additional exploratory analyses may be performed as deemed appropriate after review of the pre-specified analyses. Log transformations or nonparametric tests may be applied to measurements displaying a significant degree of non-normality.
- Listings will be provided of all data collected in the eCRFs.

3. ANALYSIS PLAN

3.1. Subject Disposition and Baseline Characteristics

3.1.1. Disposition

The number of subjects in each of the following subsets will be presented by cohort and overall.

- Full analysis set
- Responding analysis set
- Discontinued study treatment (overall and by reason)
- Discontinued study (overall and by reason)
- Follow-up status

A listing of full analysis set subjects will be provided that includes starting dose level, study center, subject number, consent date, first treatment date, duration of study treatment, and reason for treatment discontinuation

The number and percent of full analysis subjects by starting dose level will be summarized.

3.1.2. Demography and Baseline Characteristics

Baseline characteristics will be listed and will be summarized for the full analysis set as follows:

- Demographics (age, sex, race, and ethnicity) and physical characteristics (weight in kg, height in cm, and body mass index [BMI] in kg/m^2)

- Number and percent of subjects by baseline Eastern Cooperative Oncology Group (ECOG) performance status
- Number and percent of subjects having Medical Dictionary for Regulatory Activities (MedDRA) coded medical history conditions by System Organ Class (SOC) and Preferred Term (PT).
- Years from date of diagnosis for primary disease to Day 1 of protocol therapy
- Number of regimens of prior systemic therapy for cancer
- Time from completion of last prior regimen of systemic therapy for cancer to Day 1 of protocol therapy
- Number of episodes of prior radiation for cancer
- Number of prior transfusions
- Number of prior transplants
- FLT3 allelic ratio
- Internal tandem duplication (ITD) insertion length
- Peripheral AML blast count
- Peripheral AML blast percentage
- Peripheral blood white blood count
- Peripheral blood ANC
- Peripheral blood platelet count
- Peripheral blood hemoglobin
- Bone marrow aspirate blast percentage by morphology/immunohistochemistry
- Bone marrow aspirate blast percentage by flow cytometry
- Baseline TLS risk status

3.2. Protocol Deviations

Details of protocol deviations will be provided in a listing.

3.3. Study Drug Exposure and Concomitant Medications

The analysis population for study drug exposure and concomitant medications is the full analysis set.

Concomitant medications other than cancer treatment will be summarized by starting dose level and by World Health Organization Drug Dictionary (WHODRUG) Anatomical-Therapeutic-Chemical (ATC3) Term and Preferred Drug Name (ATC2 Term will be used for any investigational medications or medications not having ATC3).

Data regarding LAM-003 administration is to be categorized by starting dosing level.

The LAM-003 Dosing Log eCRF records actual dose administration from Cycle 1 Day 1 through to the last day of LAM-003 administration, including all dose modifications (increases, reductions, delays, or interruptions) and reasons for modification.

The actual length of Cycle *n* may be calculated as follows from the dates recorded on the visit eCRF.

$$Length\ of\ Cycle\ = End\ Date\ of\ Cycle\ -\ Start\ Date\ of\ Cycle\ +\ 1$$

where the End Date of Cycle is the last date of drug administration in that cycle if no subsequent cycle is administered, or is the last date before the start date of the next cycle if a subsequent cycle is administered.

3.3.1. Study Drug Administration and Compliance

The following summaries of treatment cycles will be provided:

- Number and percent of subjects by number of cycles administered, where a cycle is considered to be administered if ≥ 1 dose is received during the cycle
- Number and percent of subjects by number of completed cycles, where a cycle is considered to be completed if either (a) dosing has begun in the following cycle, or (b) the subject has completed the end-of-treatment visit.
- Number and percent of subjects by number of prolonged cycles, where a cycle is considered to be prolonged if the cycle is > 28 days in duration.
- Prescribed and actual dosing will be summarized by descriptive statistics for the following:
- Number of doses prescribed (defined as the number of cycles started × 28)
- Number of doses of actual treatment (defined as the total number of doses actually administered by the clinic staff and self-administered by the subject)
- Dose modifications and interruptions will be summarized as follows:
- Number and percent of subjects having a dose interruption
- Number and percent of subjects by reason for dose interruption
- Descriptive statistics for the number of days to the first dose interruption (for subjects having a dose interruption)
- Number and percent of subjects having a dose reduction
- Number and percent of subjects by reason for dose reduction
- Descriptive statistics for the number of days to the first dose reduction (for subjects having a dose reduction)
- Number and percent of subjects having a dose increase
- Number and percent of subjects by reason for dose increase
- Descriptive statistics for the number of days to the first dose increase (for subjects having a dose increase)

The following definition will be used to calculate compliance rate for each subject.

$$Compliance\ rate = 100 * \frac{Actual\ number\ of\ days\ on\ which\ a\ full\ dose\ was\ received}{Expected\ number\ of\ days\ on\ which\ a\ full\ dose\ was\ to\ be\ received},$$

Where:

$$Expected\ number\ of\ days = Date\ of\ last\ dose\ -\ Date\ of\ first\ dose + 1.$$

Descriptive statistics for the compliance rate will be provided.

Study drug administration data will be listed.

3.3.2. Prior and Concomitant Medications

Medication use and other therapies are collected on 6 eCRFs:

- Prior Anti-Cancer Therapy
- Prior and Concomitant Medications
- Prior Radiation Therapy
- Non-Drug Treatments/Procedures
- Prior Therapy Transplants
- Prior Transfusion History

Medications collected on the Prior Anti-Cancer Therapy and Prior and Concomitant Medications eCRFs will be coded by means of the World Health Organization Drug Dictionary (WHODrug) to WHODrug preferred drug name.

Prior anti-cancer therapies will be summarized by descriptive statistics for the number of prior regimens per subject, best response, duration of treatment, type of therapy, and the time in years from the end of the last therapy to date of the first dose of LAM-003. The Prior Anti-Cancer Therapy eCRF also will be summarized by a listing containing the verbatim medication term, WHODrug preferred drug name, therapy start and end dates, study drug start date, duration of therapy, type of therapy, and best overall response (BOR).

Prior radiation therapy will be summarized by number of treatments per subject.

Data from the, Prior Radiation Therapy, Non-Drug Treatments/Procedures, Prior Therapy Transplants, and Prior Transfusion eCRFs will be listed. The Non-Drug Treatment Procedures listing will also include the MedDRA SOC and PT terms.

Medications collected on the Prior and Concomitant Medications eCRF will be presented as a listing containing the verbatim medication term, WHODrug preferred drug name, start and end dates and study days, indication, duration of therapy, and flags to indicate if the medication was prior, concomitant, or both. The following conventions will be used:

- Prior medications are medications having a start date prior to the date of the first dose of study drug.
- Concomitant medications are medications having a start on or after the date of the first dose of study drug.

- A medication can be both prior and concomitant.

Additional descriptions of supportive care (eg, anti-diarrheal drug administration) may be provided as deemed appropriate after review of the concomitant medication data.

3.4. Safety

The analysis population for safety is the full analysis set.

3.4.1. Adverse Events

AEs are recorded by the site in the eCRFs. AEs will be summarized and listed.

AEs will be classified using MedDRA with descriptions by SOC and PT. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The eCRFs also identify the following characteristics of each AE:

- The start date and end dates of the AE
- The outcome of the AE (Fatal, Not Recovered or Not Resolved, Recovered or Resolved, Recovered or Resolved with Sequelae, Unknown)
- The relationship of the AE to study treatment (Related or Unrelated)
- The action taken regarding the study treatment (Dose Not Changed, Dose Reduced, Drug Interrupted, Drug Withdrawn, Dose Increased, Not Applicable, Unknown)
- Whether the AE was a DLT (as defined in Section 6.2.5 of the study protocol)
- Whether the AE was an SAE (as defined in Section 8.1.2 of the study protocol)
- Whether the AE was an AESI (as defined in Section 8.1.5 of the study protocol)

All DLTs, including those defined by laboratory toxicity grades, are to be recorded as AEs.

Verbatim AE terms will be coded into MedDRA SOC and PT (using MedDRA Version 19 or higher).

TEAEs are defined as AEs having a start date on or after the date of the first dose of study drug. The focus of AE summarization will be on TEAEs. AEs that occur before the first dose of study drug administration or > 30 days after the final study drug administration will be included in data listings.

An overview summary will be provided of the number and percent of subjects in each of the following categories: ≥ 1 AE; ≥ 1 TEAE; ≥ 1 TEAE of Grade ≥ 3; ≥ 1 study-drug-related TEAE; ≥ 1 study-drug-related TEAE of Grade ≥ 3; ≥ 1 SAE; ≥ 1 treatment-emergent SAE; ≥ 1 study-drug-related treatment-emergent SAE; ≥ 1 AE leading to study drug withdrawal; ≥ 1 AE leading to study drug interruption or reduction; and ≥ 1 AE leading to death.

The following summaries of AEs will be provided by starting dose and overall:

- TEAEs by SOC and PT

- Study-drug-related TEAEs by SOC and PT
- Cycle 1 DLTs by SOC and PT
- TEAEs leading to study drug interruption by SOC and PT
- TEAEs leading to study drug reduction and/or dose modification by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- Treatment-emergent SAEs by SOC and PT
- Treatment-emergent AESIs by SOC and PT
- TEAEs that are Grade 3, 4, or 5 in severity

SOCs and PT in summaries will be displayed in order of decreasing total frequency of AEs. Summaries by SOC and PT will count subjects at most once for each SOC/PT. Summaries by SOC, PT, and severity grade at most once for each SOC/PT at the highest severity experienced.

Listings of all AEs, SAEs, AESIs, AEs that led to study drug discontinuation, and AEs leading to death will be provided. Separate listings and summaries will be prepared for long-term follow-up safety data.

Hematologic abnormalities reported as AEs that were coded to preferred terms in the Blood and Lymphatic Systems Disorders SOC have been mapped to the appropriate laboratory preferred term in the Investigations SOC for summary counts in relevant tables and listings, including the following:

- Thrombocytopenia = Platelet count decreased
- Neutropenia = Neutrophil count decreased
- Leukopenia = White blood cell count decreased
- Lymphopenia = Lymphocyte count decreased
- Anemia = Hemoglobin decreased

Any additional terms added to this list will be noted in the CSR.

Abnormalities reported as AEs that were coded to preferred terms in the Metabolism and nutrition disorders SOC have been mapped to the appropriate laboratory preferred term in the Investigations SOC for summary counts in relevant tables and listings, including the following:

- Hyperglycaemia = Blood glucose increased
- Hypernatraemia = Blood sodium increased
- Hyperphosphataemia = Blood phosphorus increased
- Hyperuricaemia = Blood uric acid increased
- Hypoalbuminaemia = Blood albumin decreased
- Hypocalcaemia = Blood calcium decreased
- Hypogammaglobulinaemia = Immunoglobulins decreased

- Hypoglycaemia = Blood glucose decreased
- Hypokalaemia = Blood potassium decreased
- Hyponatraemia = Blood sodium decreased

Any additional terms added to this list will be noted in the CSR.

3.4.2. Laboratory Data

Laboratory results are recorded by the site in the eCRFs. Laboratory results will be summarized and listed.

All laboratory data will be reported using conventional units. Severity grades will be programmatically calculated using standard American Medical Association's (AMA) laboratory normal ranges [AMA 2020] and the quantitative NCI CTCAE 4.03 criteria (when available for a specific laboratory abnormality). Laboratory values considered to be normal by CTCAE criteria, meaning they do not qualify as Grade 1 - 4, will be assigned a severity grade of 0. For laboratory tests without any CTCAE criteria, toxicity grades will be recorded as 99. For parameters for which a CTCAE scale does not exist, reference ranges from the laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that occurs or continues in the period from the first study drug administration to 30 days after the last study drug administration. Any post-baseline abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent. Laboratory abnormalities that occur before the administration of study drug or > 30 days after the final administration of study drug will be included in data listings but not in summary tables.

The incidence of CTCAE treatment-emergent laboratory abnormalities will be summarized by laboratory category (eg, hematology, chemistry), laboratory parameter, and CTCAE severity grade, when applicable. The summary will present the number and percent of subjects in each category. Subjects will be characterized only once for a given study or parameter, based on the worst post-baseline severity grade observed. For parameters for which a CTCAE scale does not exist, the incidence of treatment-emergent laboratory abnormalities will be summarized by laboratory category (eg, hematology, chemistry), laboratory parameter, and number going from normal to high, and those going from normal to low.

Hematological and serum biochemistry data will be summarized in tables and may be summarized in figures showing values over time, if informative. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or during a cycle).

Shift tables for hematology and serum biochemistry data will also be presented by showing change in CTCAE severity grade from baseline to each time point. For parameters for which a

CTCAE scale does not exist, shift tables will be presented showing change in results from baseline (normal, low and high [or abnormal]) to each time point (normal, low and high [or abnormal]). For selected variables of interest, tables may be prepared to show frequencies adjusted for baseline values; for these frequencies, subjects with the same or worse grade at baseline are not considered.

All laboratory data will be displayed in listings. Values meeting CTCAE severity criteria, outside of normal ranges, or assessed as abnormal will be flagged in the listings.

3.4.3. Vital Signs and Oxygen Saturation

Vital signs are assessed at Screening, C1D1 (predose, and at 1, 2, 4, 6, and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D3, C1D4, C1D5, C1D8 (predose, and at 1, 2, 4, 6, and 8 hours postdose), and at End of Therapy.

Vital sign data and oxygen saturation data are recorded by the site in the eCRFs. Vital sign data and oxygen saturation data will be listed. Blood pressure data will be specifically categorized in terms of systolic and diastolic blood pressures. Reference ranges will be used to determine programmatically if a vital sign is below, within, or above the normal range. Normal ranges for vital signs will be referenced as follows:

- Systolic blood pressure (> 90 mm Hg and < 140 mm Hg),
- Diastolic blood pressure (> 50 mm Hg and < 90 mm Hg)
- Pulse (≥ 50 bpm and ≤ 100 bpm)
- Temperature (≤ 37.5°C)
- Oxygen saturation (> 92%)

The listings will include the normal range categories described above.

3.4.4. Electrocardiography

ECGs will be collected at Screening, C1D1 (predose [in triplicate, at least 5 minutes apart], and at 1, 2, 4, 6, and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose, and at 1, 2, 4, 6, and 8 hours postdose), C2D1, and at End of Therapy.

ECG data are recorded by the site in the eCRFs. ECG data will be summarized and listed.

The following qualitative measurements are to be recorded for each ECG:

- Overall Result (Normal/Abnormal)
- If Abnormal, was the abnormal result clinically significant? (Yes/No)

The Overall Result of Normal or Abnormal will be summarized by the following shift tables:

- Predose and End-of-Treatment measurements: Shift from baseline to worst post-baseline result
- Cycle 1 Day 1 measurements: Shift from Cycle 1 Day 1 predose result to worst postdose result

- Cycle 1 Day 8 measurements: Shift from Cycle 1 Day 8 predose result to worst postdose result

Sites are also to record the following quantitative measurements for each ECG:

- Heart Rate (bpm)
- RR Interval (msec)
- PR Interval (msec)
- QRS Duration (msec)
- QT Interval (msec)

The quantitative ECG parameters (Heart Rate, RR, PR, QRS, QT, and QTcF) will be summarized by descriptive statistics as follows:

- Predose and End-of-Treatment measurements: observed and change from baseline values at each cycle day and at End of Treatment
- Cycle 1 Day 1 measurements: observed and change from Cycle 1 Day 1 predose values at each timepoint
- Cycle 1 Day 8 measurements: observed and change from Cycle 1 Day 8 predose values at each timepoint

If not recorded by the site, the QT with Fridericia correction (QTcF) will calculated from the recorded measurements using the following formula:

- $QTcF = QT/(RR)^{1/3}$

If the RR Interval value is missing, but the Heart Rate value is present, then RR in the QTcF formula will be replaced by 60,000/Heart Rate.

QTcF categories will be summarized as follows:

- Predose and End-of-Treatment measurements: QTcF interval category at each visit
- Cycle 1 Day 1 measurements: QTcF interval category at each timepoint
- Cycle 1 Day 8 measurements: QTcF interval category at each timepoint

QTcF categories also will be summarized by shift tables as follows:

- Predose and End-of-Treatment measurements: Shift from baseline QTcF category at each visit
- Cycle 1 Day 1 measurements: Shift from Cycle 1 Day 1 predose QTcF category at each timepoint
- Cycle 1 Day 8 measurements: Shift from Cycle 1 Day 8 predose QTcF category at each timepoint

These categorical changes in QTcF will be summarized as follows:

- Predose and End-of-Treatment measurements: QTcF change from baseline value at each cycle day and at End of Treatment

- Cycle 1 Day 1 measurements: QTcF change from Cycle 1 Day 1 predose value at each timepoint
- Cycle 1 Day 8 measurements: QTcF change from Cycle 1 Day 8 predose value at each timepoint

The QTcF data will be categorized separately into the following classifications and summarized by time point:

- QTcF interval ≤ 450 msec
- QTcF interval > 450 msec and ≤ 480 msec (Grade 1)
- QTcF interval > 480 msec and ≤ 500 msec (Grade 2)
- QTcF interval > 500 msec (Grade 3)

The change of the QTcF values obtained by using the Fridericia correction will also be categorized separately as follows:

- QTcF interval change from baseline by ≤ 30 msec
- QTcF interval increases from baseline by > 30 msec and ≤ 60 msec
- QTcF interval increases from baseline by > 60 msec

QTcF data will be presented in shift tables consistent with these categories.

3.4.5. Body Height, Body Weight, and Performance Status

Body height, body weight, and ECOG performance status data are recorded by the site in the eCRFs. All body height, body weight, and ECOG performance status data will be presented in listings.

3.4.6. Other Clinical Variables Relating to Safety

3.4.6.1. Body Mass Index (BMI)

The BMI in kg/m^2 at baseline will be calculated using baseline body height and body weight data. Baseline BMI will be listed.

3.4.6.2. Pregnancy Tests

The results of pregnancy tests are recorded by the site in the eCRFs. The results of pregnancy test results at each visit will be listed.

3.4.6.3. Serum Virology

The baseline serum virology test results are recorded by the site in the eCRFs. These data will be listed.

3.4.6.4. Ophthalmological Testing

Ophthalmological results from testing performed by consulting ophthalmologists are recorded on study-specific worksheets. The data on these worksheets is recorded by the site in the eCRFs.

Results of eye exams will be listed for Visual Symptoms, Snellen Visual Acuity, Full Field Electroretinography, Multifocal Electroretinography, Tonometry, Optical Coherence Tomography, and Eye/Slit Lamp Exam.

3.5. Pharmacodynamics

Pharmacodynamic analyses will be performed by the study sponsor and are not described in this SAP.

3.6. Pharmacokinetics

Pharmacokinetic analyses will be performed by the study sponsor and are not described in this SAP.

3.7. Efficacy

Peripheral blood and bone marrow findings are the central bases for efficacy assessments in patients with AML. In support of efficacy assessments, peripheral blood hematology data are recorded by the sites in the eCRFs. In addition, peripheral blood and bone marrow samples are sent from the sites for processing and analysis at a central laboratory; data from the central laboratory are transferred electronically to Ce3, Inc.

Listings will be provided for all efficacy data collected, including data collected for peripheral blood hematological and bone marrow used for tumor assessments. The following parameters will be listed for each subject and efficacy assessment time point:

- Peripheral AML blast count
- Peripheral AML blast percentage
- Peripheral blood white blood count
- Peripheral blood ANC
- Peripheral blood platelet count
- Peripheral blood hemoglobin
- Bone marrow aspirate blast percentage by morphology/immunohistochemistry
- Bone marrow aspirate blast percentage by flow cytometry

3.7.1. Categorical Tumor Assessment Variables

For each tumor assessment, the sponsor medical monitor will categorize tumor response. In addition, for each subject, the medical monitor will determine the best overall response (BOR) considering the results across all tumor assessments. Based on the relevant criteria for AML [Cheson 2003, Döhner 2017], the possible categories for each time point and for the BOR are:

- Complete response (CR)
- Complete remission without minimal residual disease (CR_{MRD-})
- Complete response with incomplete count recovery (CRi)

- Partial response (PR)
- Treatment failure (TF)
- Disease recurrence or progression (DRP)
- Nonevaluable (NE)

Listings describing the by-time-point tumor assessment and BOR for each subject will be provided.

The BOR assessment will be used to calculate an overall remission rate (ORR) and composite complete remission (CRc) rate for each starting dose cohort and overall. ORR and CRc rate have the following definitions:

$$ORR = 100 * \frac{Number\ of\ subjects\ with\ BOR\ of\ CR, CR\text{MRD-}, CRi,\ or\ PR}{Total\ number\ of\ subjects}$$

$$CRc\ rate = 100 * \frac{Number\ of\ subjects\ with\ BOR\ of\ CR, CR\text{MRD-}, or\ CRi}{Total\ number\ of\ subjects}$$

All subjects (including those with a BOR of NE) are included in the denominators in these calculations. For all analyses of response rates, the relevant CIs will be presented.

3.7.2. Time-to-Event Tumor Control and Survival Endpoints

The time-to-event endpoints measured in this study are defined in terms of the following dates, which will be listed for each subject:

- Date of first LAM-003 dose as recorded on the LAM-003 Dosing Log eCRF
- Date of first response (for subjects with a BOR of CR, CR MRD-, CRi, or PR)
- Date of first DRP
- Date of first TF
- Date of last non-DRP response assessment (with assessment of CR, CR$_{MRD-}$, CRi, or PR)
- Date of first initiation of another therapy identified by sponsor as being an antitumor treatment administered concomitantly or after study treatment (not including hydroxyurea, cyclophosphamide, or cytarabine started at baseline or during Cycle 1 of study therapy)
- Date of death as recorded on the End of Study Page eCRF
- Date last known alive (for subjects not having a date of death) as recorded on the Post-Treatment Survival eCRF, or date of last visit if date last known alive is missing

The following time-to-event endpoints will be calculated for each subject and displayed in listings.

- Time to response (TTR) = date of first response - date of first LAM-003 dose + 1 (TTR will only be calculated for subjects having a BOR of CR, CR$_{MRD-}$, CRi, or PR)
- Duration of response (DOR) = min (date of first DRP, date of death) – date of response + 1 (DOR will only be calculated for subjects having a BOR of CR, CR$_{MRD-}$, CRi, or PR)

- Event-free survival (EFS) = min (date of first DRP, date of first TF, date of death) - date of first LAM-003 dose + 1
    - Overall survival (OS) = date of death - date of first LAM-003 dose + 1

For time-to-event endpoints having missing dates, the censoring rules described in Table 3 will be applied.

Table 3: Censoring Rules for Time-to-Event Endpoints

Endpoint	Censor Condition	Censoring Date = Minimum of Indicated Dates				
		Date of Last Non-DRP Assessment	Date of DRP	Date of Last Assessment	Date of Initiation of Other Antitumor Treatment	Date Last Known Alive
TTR	None					
DOR	Surviving and no DRP			X	X	
	Either DRP or death preceded by 2 missing or NE tumor assessments	X				
EFS	Surviving and no DRP or TF			X	X	
	Either DRP or death preceded by 2 missing or NE tumor assessments	X				
OS	Surviving					X

Abbreviations: DOR = duration of response, DRP = disease recurrence or progression, EFS = event-free survival, NE = nonevaluable, OS = overall survival, TF = treatment failure, TTR = time to response

Time-to-event endpoints will be described in the appropriate analysis sets using Kaplan-Meier methods with appropriate censoring. Medians, ranges, and relevant corresponding CIs will be presented.

4. REFERENCES

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5. TABLES, FIGURES, AND LISTINGS

A separate document will be maintained that identifies all tables, figures, and listings to be provided. This document will be updated as appropriate during development of tables, figures, and listings.