AI Therapeutics

CLINICAL STUDY PROTOCOL

Protocol Title	A Phase 1 Dose-Escalation Study of LAM-003 in Patients with Acute Myeloid Leukemia
Study Sponsor	AI Therapeutics, Inc. (formerly LAM Therapeutics, Inc.) 530 Old Whitfield St Guilford CT, 06437
Investigational Product	LAM-003
Protocol Number	LAM-003-HEM-CLN02
Developmental Phase	Phase 1b
US IND Number	112055
Protocol Versions (Dates)	Version 1 – Original (27 Sep 2017) Version 2 (19 Nov 2017) Version 3 (17 Feb 2018) Version 4 (15 Jun 2018) Version 5 (2 Jul 2018) Version 6 (10 Sep 2018) Version 7 (11 Jun 2019) Version 8 (4 Nov 2019)

Confidentiality Statement

PRINCIPAL INVESTIGATOR APPROVAL PAGE

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I have reviewed the protocol. On behalf of my institution, I agree to conduct the study as outlined in the study protocol and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements.

Principal Investigator Signature **Date**

Principal Investigator Printed Name

Institution:

Address:

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AML	acute myeloid leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical (drug coding system)
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours postdose
AUC_{0-inf}	area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of last measurable concentration
AV	atrioventricular
BID	twice per day
BUN	blood urea nitrogen
CD	cluster of differentiation
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary (cells)
CI	confidence interval
CK	creatine kinase
Cl	clearance
CLIA	Clinical Laboratory Improvement Amendments (certification)
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
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 (enzyme)
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of remission
DRP	disease recurrence or progression
EC_{50}	half-maximal effective concentration
ECG	Electrocardiogram, electrocardiographic
eCl_{CR}	estimated creatinine clearance
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
ELN	European Leukemia Network
EU	European Union
FDA	Food and Drug Administration
FDAMA	Food and Drug Modernization Act of 1997
FDG	fluorodeoxyglucose
FL	FLT3 ligand

Abbreviation	Definition
FLT3	FMS-like tyrosine kinase-3
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practices
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVHD	graft-versus-host disease
HBc	hepatitis B core (antibody)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HSP	Heat shock protein
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IFNγ	interferon-gamma
IND	investigational new drug application
IRB/IEC	institutional review board/independent ethics committee
ITD	internal tandem duplications
IUD	intrauterine device
IV	intravenous, intravenously
JAK/STAT	Janus kinase/signal transducer and activator of transcription
Kd	equilibrium disassociation constant
LDH	lactate dehydrogenase
LLQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	nonevaluable
NGS	next-generation sequencing
NK	natural killer (cells)
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
OR	objective remission
OS	overall survival
PCR	polymerase chain reaction
PD-L1	programmed death ligand 1
PET	positron emission tomography
pKa	logarithm of the acid dissociation constant
PR	partial remission
PT	prothrombin time
QD	once per day
QTc	cardiac QT interval corrected for heart rate
QTcB	cardiac QT interval corrected for heart rate using Bazett formula
QTcF	cardiac QT interval corrected for heart rate using Fridericia formula

Abbreviation	Definition
PI3K/AKT	phosphoinositide 3-kinase/protein kinase B
RDR	recommended dosing regimen
RNA	ribonucleic acid
SAE	serious adverse event
SRC	safety review committee
SUSAR	suspected, unexpected, serious adverse reaction
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TF	treatment failure
TKD	tyrosine kinase domain
TLS	tumor lysis syndrome
T_{max}	time of maximum concentration
TTR	time to remission
ULN	upper limit of normal
US(A)	United States (of America)
V_d	volume of distribution
WHODRUG	World Health Organization Drug Dictionary
WT	wild-type
βHCG	beta human chorionic gonadotropin
λ_z	terminal elimination rate constant

PROTOCOL SYNOPSIS

Protocol Number	LAM-003-HEM-CLN02
Title of Study	A Phase 1 Dose-Escalation Study of LAM-003 in Patients with Acute Myeloid Leukemia
Investigational Product	LAM-003
US IND Number	112055
Study Background	Acute myeloid leukemia (AML) is a clonal disease characterized by the proliferation and accumulation of myeloid progenitor cells in the bone marrow, resulting in hematopoietic failure with attendant neutropenia, thrombocytopenia, and anemia. Clinical manifestations of the disease can include thrombotic complications due to leukemic blast cell hyperleukocytosis, bacterial and fungal infections, bleeding, and fatigue. The incidence is highest between 55 and 85 years of age. Of all leukemias, AML has the lowest survival rate, particularly in elderly patients, who more frequently present with poor prognostic features and cannot tolerate intensive therapy. Five-year survival rates for all patients are <30%. Current standard of care treatment in younger, fit patients who can tolerate intensive therapy is daunorubicin and cytarabine chemotherapy as induction followed by high-dose cytarabine consolidation. Allogeneic bone marrow transplantation is also used for treating poor-prognosis, high-risk disease in younger adults. In older patients, most of whom are not able to tolerate intense chemotherapy, monotherapy with low-dose cytarabine or decitabine are among the therapeutic alternatives. Unfortunately, most patients will eventually experience disease relapse and – despite use of sequential therapies to control disease manifestations – are likely to die of their cancers. FMS-like tyrosine kinase-3 (FLT3) is a cell-surface receptor that is overexpressed in nearly all cases of AML. Activating mutations in FLT3 occur in ~30% of patients and represent the most frequent genetic alteration in this disease. About 75% of the activating mutations are internal tandem duplications (FLT3-ITD) and 25% are point mutations in the activation loop of the tyrosine kinase domain (TKD) (consisting mostly of D835 mutations). Both types of mutations have been shown to constitutively activate FLT3 and are linked to a poor prognosis. Midostaurin, a FLT3 tyrosine kinase inhibitor, was recently approved as a first-line therapy in combination with standard induction chemotherapy, and other FLT3 inhibitors are in clinical development. However, resistance to these inhibitors develops through the acquisition of secondary mutations in FLT3, upregulation of other molecular pathways, or stimuli from the tumor microenvironment. Thus, novel mechanisms of action are needed to address these resistance mechanisms. Heat shock protein (HSP)90 is a highly conserved, ubiquitously expressed, molecular chaperone that plays an important role in regulating post-translational folding, stability, and function of cellular proteins (often referred to as “client proteins”). Folding of client proteins is dependent on the ATPase activity of HSP90, and inhibitors of HSP90 can result in degradation of oncogenic client proteins through the ubiquitin-proteasome pathway. Mutant FLT3 is a client protein of HSP90. Mutant FLT3 expression is associated

with higher levels of HSP90 expression in primary AML cells, and HSP90 appears to be important in mutant FLT3 stability and function.

AI Therapeutics, Inc. is developing LAM-003 as a clinical HSP90 inhibitor. LAM-003 is the L-alanine prodrug of the active moiety LAM-003A. Following oral administration, removal of L-alanine by esterases in the intestinal tract leads to systemic absorption of LAM-003A. Nonclinical studies indicate that LAM-003A demonstrates FLT3-ITD client protein degradation and cytotoxicity toward FLT3-ITD-expressing AML cell lines and primary AML cells. LAM-003 shows significant efficacy in mouse xenografts bearing the FLT3-ITD-containing MV4-11 AML cell line. Of importance, LAM-003A is also active in cells that have become resistant to FLT3-ITD inhibitors due to receptor mutation, upregulation of "work-around" pathways, or the influence of stromal cells that support AML survival and growth. LAM-003A also shows cytotoxicity toward FLT3-TKD and FLT3-wild-type (WT) AML. In cells transfected with FLT-TKD mutants, LAM-003 induced FLT3-TKD degradation and reduced cell surface expression with identical potency to FLT3-ITD. In FLT3-WT AML cell lines and patient-derived cells, many were as sensitive to LAM-003A as FLT3-ITD cell lines as measured by cytotoxicity assays. Hence, while FLT3-ITD AML is uniformly sensitive to LAM-003A, additional AML subtypes, driven by different oncogenic drivers that are client proteins of HSP90, are also sensitive. Further, LAM-003A downregulates the immunosuppressive protein, programmed death-ligand 1 (PD-L1) in AML cell lines, suggesting the potential for salutary immunomodulatory effects.

Nonclinical pharmacokinetic studies indicate that LAM-003 should deliver comparable plasma exposures of LAM-003A as oral administration of LAM-003A. In vitro, LAM-003A is both a substrate and inhibitor of cytochrome P450 (CYP) 3A4. In nonclinical toxicology studies, the primary adverse effects of potential clinical relevance included gastrointestinal toxicities and lymphoid depletion.

A Phase 1 dose-ranging study of LAM-003A evaluated 26 patients with advanced solid tumors. Doses as high as 320 mg twice per day (BID) (640 mg total per day) given daily in repeated 28-day cycles were evaluated. Based on pre-established definitions of dose-limiting toxicity (DLT), an MTD was not determined. However, at total doses >600 mg per day, Grade 1-3 gastrointestinal adverse events (AEs) occurred in 10/10 subjects and Grade 1-2 recoverable vision changes of light/dark adaptation difficulty, dark/dimmed vision, white ocular crescents, and/or floaters were observed in 3/10 subjects (consistent with a known class effect for HSP90 inhibitors).

Pharmacokinetic data from the study indicated that plasma maximum concentration (C_{max}) and area under the concentration-time curve (AUC) values increased in a nearly dose-proportional manner. Day 21 exposures were 1- to 2-fold more than on Day 1, indicating modest drug accumulation. The average half-life ($t_{1/2}$) after repeated dosing was 11.2 hours, supporting once-per-day (QD) or BID dosing. The recommended starting dose level was 240 mg BID (480 mg total daily dose).

Collectively, these nonclinical and clinical data provide a foundation for development of LAM-003 to characterize the drug's safety, pharmacology, and antitumor activity in patients with AML.

Study Design

This clinical trial is a Phase 1 study evaluating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of LAM-003 across a range of dose levels when administered to subjects with previously treated relapsed or refractory AML. Subjects will self-administer oral LAM-003 QD or BID continuously in repeated 28-day cycles. Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher dose levels of LAM-003 using a standard 3+3 dose-escalation design. The initial cohort of subjects in this study will be prescribed 200 mg QD; this dose level is 2.4-fold below the recommended dosing regimen (RDR) of 480 mg total daily dose established in the prior Phase 1 study of LAM-003A in patients with solid tumors. Based on the pattern of DLTs observed in Cycle 1, escalation in this study will proceed to define an MTD and an RDR that may be at the MTD or a lower dose within the tolerable dose range.

Study Objectives

Primary Objective

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

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

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

Study Endpoints

Primary Endpoints

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

Secondary Endpoints

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 treatment-emergent adverse events (TEAEs); laboratory abnormalities; vital sign/oxygen saturation abnormalities; adverse electrocardiogram (ECG) findings; DLTs; SAEs; adverse events of special interest; or 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)
- Type, frequency, and timing of use of supportive care and other concomitant medications

Pharmacokinetics

- LAM-003 and LAM-003A plasma concentrations (as measured using a validated bioanalytical assay)

- Derived LAM-003 and LAM-003A pharmacokinetic parameters (including AUC, C_{max}, time of maximum concentration [T_{max}], volume of distribution [Vd], $t_{1/2}$, terminal elimination rate constant [λz], and apparent clearance [Cl/F]) (as determined using noncompartmental methods)

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: 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 $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/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

Exploratory Endpoints

Pharmacodynamics

- Changes in 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 (FL) concentration (as measured using an immunoassay)
- Changes in 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)

Biomarkers

- Baseline AML blast FLT3 mutation type and FLT3 mutation-to-WT allele ratio
- Baseline mutational profile in AML blasts (with germ-line control in saliva) (as assessed with next-generation sequencing [NGS])

Selection and Enrollment of Study Subjects

Planned Number of Subjects

The total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all 5 planned starting dose levels and 6 additional subjects are enrolled at the MTD or RDR, as many as 36 subjects could be enrolled. If an additional dose level or an additional schedule (eg, twice-per-day [BID]) administration is explored in 6 subjects per cohort, as many as 12 additional subjects could be enrolled, bringing the potential sample size to 48 subjects. To allow for the possibility that some subjects may not be fully evaluable, up to 60 subjects may be enrolled.

Target Population

The target population comprises adult subjects with adequate performance status and organ function who have histologically confirmed AML that has progressed after appropriate prior therapy and have no potential for cure with currently available treatments.

Enrollment Criteria

Inclusion Criteria

Study candidates must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Men and women of age ≥18 years.
2) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix 14.1).
3) Current diagnosis of AML.
4) AML has been previously treated and has progressed during or relapsed after prior therapy.
5) Presence of measurable AML, defined as the presence of >5% blasts in the bone marrow (based on a bone marrow sample with ≥200 nucleated cells and bone marrow spicules) and/or >1.0 × 10^9/L blasts in the peripheral blood.

6) All acute toxic effects of any prior antitumor therapy (except hydroxyurea, cytarabine, and/or cyclophosphamide given to control blast count proliferation) resolved to Grade ≤1 before the start of study therapy (with the exception of alopecia [Grade ≤2 permitted], neurotoxicity [Grade ≤2 permitted], or bone marrow parameters [Grade 1 to 4 permitted]). ***Note: For subjects with rapidly proliferative disease, use of hydroxyurea, cytarabine, and/or cyclophosphamide is allowed before the start of study therapy and during Cycle 1, but must be discontinued thereafter.***
7) Adequate hepatic profile:
    a) Serum alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN) (Grade ≤1).
    b) Serum aspartate aminotransferase (AST) ≤3 × ULN (Grade ≤1).
    c) Serum bilirubin ≤1.5 × ULN (Grade ≤ 1).
8) Adequate renal function:
    a) Serum creatinine <1.5 × ULN (Grade 1), or
    b) Estimated creatinine clearance (eCl_{CR}) ≥60 mL/min (eCL_{CR} to be calculated by the Cockcroft-Gault formula [see Appendix 14.2]).
9) Adequate coagulation profile:
    a) Prothrombin time (PT) ≤1.5 × ULN (Grade ≤1).
    b) Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (Grade ≤1).
10) Negative antiviral serology:
    a) Negative human immunodeficiency virus (HIV) antibody.
    b) Negative hepatitis B surface antigen (HBsAg) and negative hepatitis B core (HBc) antibody or undetectable hepatitis B (HBV) deoxyribonucleic acid (DNA) by quantitative PCR testing.
    c) Negative hepatitis C virus (HCV) antibody or negative HCV ribonucleic acid (RNA) by quantitative PCR.
11) For female subjects of childbearing potential, a negative serum pregnancy test.
12) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of the screening period until ≥30 days after the final dose of study therapy. ***Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional laboratory postmenopausal range and a negative serum or urine beta human chorionic gonadotropin [βHCG]); or is menopausal (age ≥50 years with amenorrhea for ≥6 months).***
13) For male subjects who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception, willingness to use a protocol-recommended method of

contraception from the start of study therapy until ≥30 days after the final dose of study therapy and to refrain from sperm donation from the start of study therapy until ≥90 days after administration of the final dose of study therapy. ***Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.***

14) Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures (including all bone marrow biopsy/aspirations and radiographic studies), and study restrictions.
15) Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

Exclusion Criteria

Study candidates who meet any of the following criteria will not be eligible for participation in this study:

1) Peripheral blood leukemic blast cell count >50 × 10^9/L before the start of study therapy and despite the use of hydroxyurea, cytarabine, and/or cyclophosphamide.
2) Presence of known central nervous system (CNS) leukemia. ***Note: Radiographic imaging or cerebrospinal fluid analysis is not required as a condition of enrollment into the study***.
3) Presence of another cancer with disease manifestations or therapy that could adverse effect subject safety or longevity, create the potential for drug-drug interactions, or compromise the interpretation of study results.
4) Ongoing Grade >1 proliferative or nonproliferative retinopathy (eg, due to diabetes mellitus, hypertension, macular degeneration, prematurity, genetic disorder). ***Note: Subjects with resolved retinal tears due to age-related vitreous humor shrinkage are not excluded***.
5) Significant cardiovascular disease (eg, myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure; or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.
6) Significant screening ECG abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, left bundle-branch block, 2nd-degree atrioventricular (AV) block type II, 3rd-degree AV block, Grade ≥2 bradycardia, or corrected QT (QTc by Fridericia method) >480 msec (Grade >1).

7) Gastrointestinal disease (eg, gastric or intestinal bypass surgery, pancreatic enzyme insufficiency, malabsorption syndrome, symptomatic inflammatory bowel disease, chronic diarrheal illness, bowel obstruction) that might interfere with drug absorption or with interpretation of gastrointestinal AEs.
8) Uncontrolled, ongoing systemic bacterial, fungal, or viral infection (including upper respiratory tract infections) at the time of start of study therapy. ***Note: Subjects with localized fungal infections of skin or nails are not excluded. Subjects may be receiving prophylactic or therapeutic antibiotics if there is no occurrence of fever within 48 hours before starting study therapy, and if antibiotics are not proscribed due to the potential for drug-drug interactions (see Exclusion Criterion 16)***.
9) Pregnancy or breastfeeding.
10) Major surgery within 4 weeks before the start of study therapy.
11) Subject is a candidate for hematopoietic stem cell transplantation (HSCT), has an appropriate HSC donor, and is willing to undergo HSCT.
12) In subjects with prior HSCT, evidence of graft-versus-host disease (GVHD) manifesting as NCI CTCAE Version 4.03 Grade ≥2 serum bilirubin, Grade ≥3 skin involvement, or Grade ≥3 diarrhea at the start of study therapy.
13) Prior solid organ transplantation.
14) Prior HSP inhibitor therapy.
15) Ongoing immunosuppressive therapy other than corticosteroids. ***Note: At study entry, subjects may be using systemic, intraarticular, inhaled, or topical corticosteroids. During study therapy, subjects may use systemic, enteric, intraarticular, inhaled, or topical corticosteroids as required for intercurrent conditions.***
16) Use of a strong inhibitor or inducer of cytochrome P450 (CYP) 3A4 (including itraconazole, ketoconazole, posaconazole, or voriconazole) within 7 days prior to the start of study therapy or expected requirement for chronic use of a strong CYP3A4 inhibitor or inducer during Cycle 1 of study therapy (see Appendix 14.4). ***Note: For subjects requiring antifungal prophylaxis/therapy, oral fluconazole or isavuconazonium can be considered. Echinocandins (eg, caspofungin, anidulafungin, or micafungin) are also acceptable, realizing the disadvantage of the requirement for intravenous administration.***
17) Use within 7 days prior to the start of study therapy of a drug known to prolong the QT interval (see Appendix 14.5). ***Note: For subjects requiring antifungal prophylaxis/therapy, oral fluconazole is permitted given that the risk of QT prolongation is considered low (as documented in product labeling).***
18) Concurrent participation in another therapeutic or imaging clinical trial. ***Note: Subjects are not precluded from undergoing evaluations involving observation, noninvasive diagnostic procedures or sampling, or questionnaires as follow-up to a prior study or as components of a concurrent noninterventional study.***

19) Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a subject's ability to provide informed consent, adversely affect the subject's ability to cooperate and participate in the study, or compromise the interpretation of study results.

Study Treatment

Study Drug Dosage Forms, Strength, Storage and Supply

The sponsor will supply LAM-003 as white, 0.25", round, convex, film-coated tablets containing 50 mg of drug substance. Inactive ingredients include: microcrystalline cellulose, lactose monohydrate, crospovidone, hydroxypropyl cellulose, colloidal silicon dioxide, sodium starch glycolate, compritol 888 ATO, Opadry clear and Opadry white. Tablets are packaged in high-density polyethylene (HDPE) bottles containing 28 tablets per bottle. During shipping and storage, bottles should remain refrigerated at temperatures of 2 to 8°C [35.6 to 46.4°F]).

Premedications

Administration of antiemetics, antidiarrheals, or medical prophylaxis for tumor lysis syndrome (TLS) should be provided as indicated in Section 6.2.1 of the protocol.

Study Drug Administration

Dose Administration, Schedule, and Dosing Conditions

In each 28-day cycle, subjects are to self-administer LAM-003 starting on Day 1 and then continuously thereafter (28 total doses/cycle). Subjects should take the study drug at approximately the same time each day, ideally at ~24-hour intervals (eg, ~8AM every day) for the planned QD schedule or at 12-hour intervals (eg, ~8AM and ~8PM every day) if a BID schedule is evaluated. In conjunction with frequent pharmacokinetic assessments on C1D1, C1D2, and C1D8, subjects should take the drug at the study center under the supervision of study personnel and the timing of drug administration must be documented in the clinic notes and/or in the subject diary. While variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

At each dose administration, the number of LAM-003 tablets corresponding to the appropriate doses of each drug should be swallowed whole with 100 to 200 mL (~4 to 8 ounces) of water. Subjects should be instructed not to bite or chew on the tablets. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.

In conjunction with frequent pharmacokinetic assessments on C1D1, C1D2, and C1D8, subjects should ingest the drug while fasting (defined as no food with the exception of clear liquids for ≥2 hours before and ≥1 hour after dosing). Pending the evaluation of the effect of food on LAM-003 absorption, subjects are encouraged to take the drug while fasting on other days.

Starting Dose Levels

Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher starting dose levels of LAM-003 using a standard 3+3 design, as indicated in Table S-1. The initial cohort of subjects will be 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 TEAE requiring dose modifications to levels below Dose Level 1.

Table S-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
Abbreviations: QD=once per day		

The following dose-escalation rules will be employed, considering DLTs observed in Cycle 1 of therapy:

- Each dose level cohort will initially enroll 3 subjects.
- If 0 of the first 3 subjects has a DLT, the next cohort of 3 subjects will be treated at the next higher dose level.
- If 1 of the first 3 subjects in a cohort experiences a DLT, an additional 3 subjects will be treated at that same dose level. If 0 of the additional 3 subjects experience a DLT, the next cohort of 3 subjects will be treated at the next higher dose level.
- If ≥2 of 3 or ≥2 of 6 subjects experience a DLT, the MTD will have been exceeded and 3 more subjects will be treated at the next lower dose level (if only 3 subjects were previously treated at that prior dose level). If 6 subjects were previously treated at the prior dose level, that prior dose level will provisionally be considered the MTD.
- An additional 6 subjects (up to 12 total) may be enrolled at the MTD or RDR.
- With the concurrence of the Safety Review Committee (SRC) (comprising the investigators and clinical representatives of the sponsor), additional subjects (up to 12 subjects per dose level) may be accrued at dose levels at or below the MTD to refine the estimation of the RDR and further define the pharmacology of LAM-003. Such accrual may occur:
  - At Dose Level -1 or -2 (100 or 50 mg of LAM-003, respectively).
  - At an initially planned dose level (as indicated in Table S-1) or at a dose level that lies between the initially planned dose levels.
  - Using an alternative schedule (eg, BID) with a total daily dose that does not exceed the total daily MTD (rounded up or down to the nearest even multiple of 50 mg).

The following additional procedures will be followed during the dose escalation:

- The first subject to be treated at Dose Level 1 will be observed for ≥1 week after initiation of LAM-003 before any subsequent subjects are treated at the same dose level.

- Each group of 3 subjects within a cohort must receive ≥75% (21/28 doses for a QD schedule or 42/56 doses for a BID schedule) of planned Cycle 1 LAM-003 doses per subject and must be observed for a minimum period of ~4 weeks throughout this treatment period without DLT before subsequent subjects are enrolled at the next higher dose level. Any subject without DLT who does not complete these requirements may be replaced.
- Escalation to the next dose level can only occur upon review of the safety data from all ongoing and previous subjects and with the concurrence of the SRC.
- Intrasubject dose escalation above the initially assigned dose level will be permitted as defined in Section 6.2.7 of the protocol.
- Accrual of additional subjects to a treatment cohort may be considered by the SRC with the concurrence of the study sponsor.

Definition of DLTs

The SRC will meet when each cohort has completed Cycle 1 and will review safety, and any available pharmacokinetic or pharmacodynamic data. The sponsor, working in consultation with the investigators and SRC, will determine whether a TEAE meets a definition of DLT as defined in the protocol. Reference will be made to the CTCAE, Version 4.03, for grading the severity of TEAEs, treatment-emergent laboratory abnormalities, and DLTs, considering the known safety profiles of the study drug and other medical factors.

The existing clinical experience indicates that nausea, vomiting, diarrhea, tachycardias, respiratory distress, and visual disturbances can occur in association with LAM-003A administration and may be dose-limiting at total daily doses >600 mg. Visual symptoms observed with LAM-003A have included darkening or dimming of vision, difficulties with light/dark adaptation, appearance of intermittent bilateral white ocular crescents, and visual floaters. Dose-dependent ocular symptoms described with other HSP90 inhibitors have included visual dimming, difficulties with light/dark adaptation, nyctalopia (night blindness), photopsia (perceived flashes of light), photophobia (light sensitivity), and blurred vision.

Based on this information but considering the limited experience with LAM-003/LAM-003A, DLTs for the purposes of establishing the MTD and RDR in this study will be defined as any of the following TEAEs occurring in Cycle 1 of LAM-003 therapy that cannot be considered incontrovertibly related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication:

- Grade 4 neutropenia persisting for ≥28 days
- Grade ≥3 vomiting despite recommended antiemetic support
- Grade ≥3 diarrhea despite recommended antidiarrheal support
- Grade ≥2 visual disturbances
- Grade ≥2 heart failure or ventricular dysfunction
- Grade 3 TLS despite adequate prophylaxis (unless TLS results in no Grade ≥2 renal dysfunction or other Grade ≥2 end-organ injury and resolves ≤7 days from onset)

- Grade 4 TLS despite adequate prophylaxis
- Other Grade ≥3 nonhematological AEs (with the exception of asymptomatic Grade ≥3 laboratory abnormalities that improve to Grade ≤2 within 72 hours)
- The occurrence of either of the following circumstances during Cycle 1:
  - Inability to comply with ≥75% (21/28 doses for a QD schedule or 42/56 dose for a BID schedule) of planned LAM-003 doses due to an AE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication
  - Following a dose interruption starting in Cycle 1, failure to recover to baseline within 2 weeks from the last dose of LAM-003 due to a TEAE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication; occurrence of such a TEAE should also result in permanent discontinuation of study drug (see Section 6.5)

Definitions of MTD and RDR

The MTD is the highest tested dose level at which ≥6 subjects have been treated and which is associated with a Cycle 1 DLT in ≤17% of the subjects. The RDR may be the MTD or may be a lower dose within the tolerable dose range. Selection of the RDR will be based on consideration of short- and long-term safety information together with available pharmacokinetic, pharmacodynamic, and efficacy data.

Duration of Therapy

Subjects may receive study therapy until the earliest of any of the following events: subject request to withdraw from study treatment; documented objective evidence of treatment failure or of AML relapse or progression while receiving study treatment at the highest individually tolerated dose level; for a subject in PR, continued red blood cell transfusion dependence at Week 20; intolerable toxicity despite appropriate supportive care and/or dose modification; failure to recover to Grade ≤1 or baseline within 2 weeks from the last dose of LAM-003 following interruption for a TEAE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication; the development of intercurrent illness or other substantial change in the subject's condition or circumstances that would place the subject at unacceptable risk as determined by the study investigator in consultation with the medical monitor; initiation of treatment for the subject's cancer with an off-study therapeutic regimen; pregnancy or breastfeeding; substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results; discontinuation of the study by the study center, the study sponsor, relevant regulatory agencies, or the IRB/IEC.

Statistical Methods

Analysis Conventions

Analysis Sets

Appropriate data analysis sets will be defined. The full-analysis set will include data from all subjects who receive ≥1 dose of study therapy. Other analysis sets (responder and evaluable analysis sets) will be defined, as appropriate, and will include data from subjects who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest.

Data Handling

Data will be described and summarized by dosing regimen and cohort.

Descriptive summaries for continuous variables will contain N (number in population); n (number with data); mean (with standard deviation and confidence intervals [CIs] on the mean); median; minimum; and maximum. Descriptive summaries for categorical variables will include N, n, percentage, and CIs on the percentage.

The baseline value used in each analysis will be the last (most recent) predose value. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the most extreme change from baseline during the study will also be described and summarized. Shift tables or graphical techniques (eg, bar charts, line graphs) may be used when such methods are appropriate and informative.

Data from all participating study centers will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate. Unless otherwise indicated, CI for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Unless otherwise specified, statistical testing will be 2-sided at a nominal 0.05 level of significance. Given the exploratory nature of this study, adjustments for multiple comparisons need not be applied.

Analysis Plan

Subject Disposition and Baseline Characteristics

Based on the full-analysis set, information regarding subject disposition, demographics, cancer history, tumor characteristics, and other baseline characteristics will be described.

Study Drug Exposure, Concomitant Medications, and Safety

Study drug administration and compliance, concomitant medication use, supportive care use, AEs, laboratory abnormalities, vital signs/oxygen saturation, body weight, and ECOG performance status will be described and summarized. For safety analyses, AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Standard regulatory definitions of seriousness will be applied to AEs. Laboratory abnormalities will be graded according to CTCAE severity grade whenever applicable.

Quantitative and qualitative ECG assessments of rhythm abnormalities, cardiac intervals, wave form abnormalities, and ectopy will be reported.

Concomitant medication use will be coded using the World Health Organization Drug Dictionary into Anatomical Therapeutic-Chemical classification (ATC) codes; data descriptions may particularly focus on supportive medications and care provided in response to any study-therapy-induced adverse effects and any drugs that might represent a risk for a CYP3A4-mediated drug-drug interaction.

Pharmacokinetics

Noncompartmental methods will be used to derive pharmacokinetic parameters. LAM-003A concentrations and derived pharmacokinetic parameters will be described and will be summarized using appropriate graphical and tabular methods. Dose-exposure relationships will be characterized.

Efficacy

Efficacy analyses will be based on the full-analysis and responder data sets. Tumor response and progression will be assessed using standard response and progression criteria for AML as adapted to this protocol. Response rates will be presented with relevant CIs. Time-to-event endpoints will be summarized using Kaplan-Meier methods with appropriate censoring. Medians, ranges, and corresponding CIs will be presented.

Other Analyses

Using appropriate regression techniques, possible relationships between subject characteristics (eg, sex, race, age, weight, tumor characteristics, dose) and outcome measures (eg, pharmacokinetic parameters, pharmacodynamic parameters, efficacy) may be assessed. Similarly, associations between outcome measures (eg, relationships between pharmacokinetic and pharmacodynamic parameters) may be evaluated.

Basis for the Planned Sample Sizes

In the dose escalation, the cohort sizes of 3 to 6 subjects allow evaluation of regimen safety using a standard definition of MTD (ie, a starting dose associated with DLT in ≤17% of subjects during the first cycle of therapy). Based on the planned 3+3 dose-escalation scheme, there is a high probability of dose escalation to the next dose level if the true underlying proportion of DLT is low at the current dose level. Conversely, there is a low probability of escalation to the next dose level if the true underlying proportion of DLT is high at the current dose level.

1 INTRODUCTION

1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a clonal disease characterized by the proliferation and accumulation of myeloid progenitor cells in the bone marrow, resulting in hematopoietic failure with attendant neutropenia, thrombocytopenia, and anemia [Liesveld 2016]. Clinical manifestations of the disease can include thrombotic complications due to leukemic blast cell hyperleukocytosis, bacterial and fungal infections, bleeding, and fatigue. Occurring predominately in adults, the incidence increases with increasing age, most commonly affecting those between 55 and 85 years of age [SEER 2017, Siegel 2017]. Of all leukemias, AML has the lowest survival rate, particularly in elderly patients, who more frequently present with poor prognostic features and cannot tolerate intensive therapy [Podoltsev 2017]. Five-year survival rates for all patients are <30% [SEER 2017].

Current standard of care treatment in younger, fit patients who can tolerate intensive therapy is daunorubicin and cytarabine chemotherapy as induction followed by high-dose cytarabine consolidation [Döhner 2017, NCCN 2017]. Allogeneic bone marrow transplantation is also used for treating poor-prognosis, high-risk disease in younger adults. In older patients, most of whom are not able to tolerate intense chemotherapy, monotherapy with low-dose cytarabine or decitabine are among the therapeutic alternatives. Unfortunately, most patients will eventually experience disease relapse and despite use of sequential therapies to control disease manifestations are likely to die of their cancers.

1.2 FMS-Like Tyrosine Kinase-3 Receptor and Ligand in AML

FMS-like tyrosine kinase-3 (FLT3) is a cell-surface receptor that dimerizes on binding its cognate ligand, the cytokine FLT3 ligand (FL), resulting in autophosphorylation and transduction of signals promoting proliferation and survival via the Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and other pathways [Lyman 1998, Janke 2014, Tsapogas 2017]. Its ligand, FL, is a cytokine that promotes the expansion of hematopoietic precursors [Tsapogas 2017]. Circulating concentrations of FL are normally low, but rise in response to chemotherapy-induced or other bone marrow aplasia [Wodnar-Filipowicz 1996].

FLT3 is overexpressed in nearly all cases of AML [Carow 1996]. Mutations in FLT3 occur in ~30% of patients and represent the most frequent genetic alteration in this disease [Papaemmanuil 2016]. About 75% of these mutations are internal tandem duplications (FLT3-ITD) and 25% are point mutations in the activation loop of the tyrosine kinase domain TKD (consisting mostly of D835 mutations) [Pratz 2017]. The mutations are activating and the presence of a FLT-ITD mutation confers an adverse prognosis [Kiyoi 1999, Thiede 2002, Schnittger 2002, Fröhling 2002]. In addition to enzyme autoactivation arising from the mutation, FLT3-ITD receptors remain highly responsive to FL and progressive increases in circulating FL following sequential regimens of myelotoxic therapy [Wodnar-Filipowicz 1996] may impair the efficacy of drugs targeting FLT3 mutations in AML [Sato 2011].

Given the importance of FLT3 in AML pathophysiology, FLT3 inhibitors have been developed and are undergoing clinical evaluation. Midostaurin, a multi-targeted tyrosine kinase inhibitor,

was recently approved as a first-line therapy in combination with standard induction chemotherapy [Stone 2017, Levis 2017]. Another clinically available multitargeted tyrosine kinase inhibitor, sorafenib, has been evaluated alone and in combination therapy in several AML treatment settings and is commonly administered off-label to patients with FLT3-mutant AML [Antar 2017]. Several potent and selective FLT3 inhibitors (eg, quizartinib, gilteritinib, crenolanib) are undergoing active clinical development as investigational agents [Garcia 2017]. Unfortunately, resistance to all of these types of inhibitors commonly develops through the acquisition of secondary mutations in FLT3, upregulation of other molecular pathways, or the influence of the bone marrow microenvironment [Ghiaur 2017]. Thus, novel drugs are needed that can circumvent these mechanisms of resistance.

1.3 Heat Shock Proteins as Clinical Targets for AML Therapy

Heat shock protein (HSP)90 is a highly conserved, ubiquitously expressed, molecular chaperone that plays an important role in regulating post-translational folding, stability, and function of cellular proteins (often referred to as "client proteins") [Nahleh 2012]. Cancer cells experience high levels of proteotoxic stress and rely upon stress-response pathways for survival and proliferation, thereby becoming dependent on stress-inducible proteins, such as HSP90. Because folding of client proteins is dependent on HSP90-mediated hydrolysis of adenosine triphosphate (ATP), inhibitors that disrupt the ATPase function of HSP90 can cause degradation of oncogenic client proteins through the ubiquitin-proteasome pathway, thereby offering a therapeutic approach to cancer.

Mutant FLT3 is a client protein of HSP90 [Minami 2002, Yao 2003, Al Shaer 2008]. Mutant FLT3 expression is associated with higher levels of HSP90 expression in primary AML cells [Reikvam 2011]. Treatment with an HSP90 inhibitor induces mutant FLT3 degradation and tumor cytotoxicity [Yao 2003, Zong 2015], leading to enhanced sensitivity of AML blasts harboring this oncogenic mutation [Zong 2015].

1.4 LAM-003/LAM-003A

Based on the collective knowledge regarding the roles of FLT3 and HSP90 in AML, AI Therapeutics, Inc. is developing LAM-003 as a clinical HSP90 inhibitor for patients with AML. The initial goal of development is to offer a novel treatment approach that can circumvent resistance in patients who have experienced failure of other drugs. Ultimately, it is hoped that LAM-003 administered alone or in combination can supplement or complement current treatment methods.

1.4.1 Background

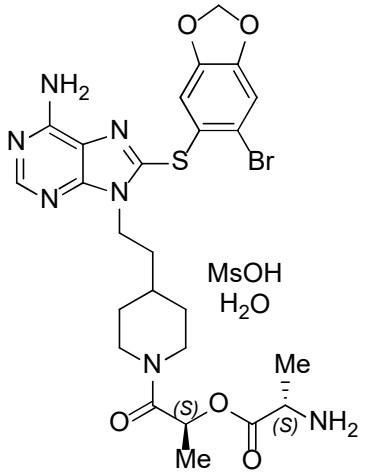
Myrexis Pharmaceuticals, Inc., Salt Lake City, Utah, USA (Myrexis) originally began development of the drug in the form of MPC-3100 (hereafter designated LAM-003A). IND-enabling nonclinical studies supported a first-in-human study of LAM-003A in 26 patients with advanced solid tumors under IND 104348. Subsequently, Myrexis began nonclinical development of a prodrug, MPC-0767 (now designated LAM-003), to enhance aqueous solubility and LAM-003A delivery. Myrexis demonstrated that LAM-003 undergoes hydrolysis to LAM-003A in the gastrointestinal tract. Nonclinical studies using a xenograft model of gastric cancer showed that oral dosing of LAM-003 had comparable antitumor activity to oral dosing of LAM-003A. Pharmacokinetic studies in mice, rats, and monkeys showed similar plasma

exposures of LAM-003A when delivered as the prodrug or the active moiety, and that exposure to the prodrug (LAM-003) in the systemic circulation was negligible. For business reasons, Myrexis did not pursue further development of LAM-003. AI Therapeutics, Inc. subsequently acquired the rights to the drug with the intent of developing LAM-003 in patients with hematological cancers.

1.4.2 Chemistry

LAM-003 has the chemical name of [(1S)-2-[4-[2-[6-amino-8-[(6-bromo-1,3-benzodioxol-5-yl)sulfanyl]purin-9-yl]ethyl]-1-piperidyl]-1-methyl-2-oxo-ethyl] (2S)-2-aminopropanoate mono-mesylate, mono-hydrate]. The structure is shown in Figure 1.

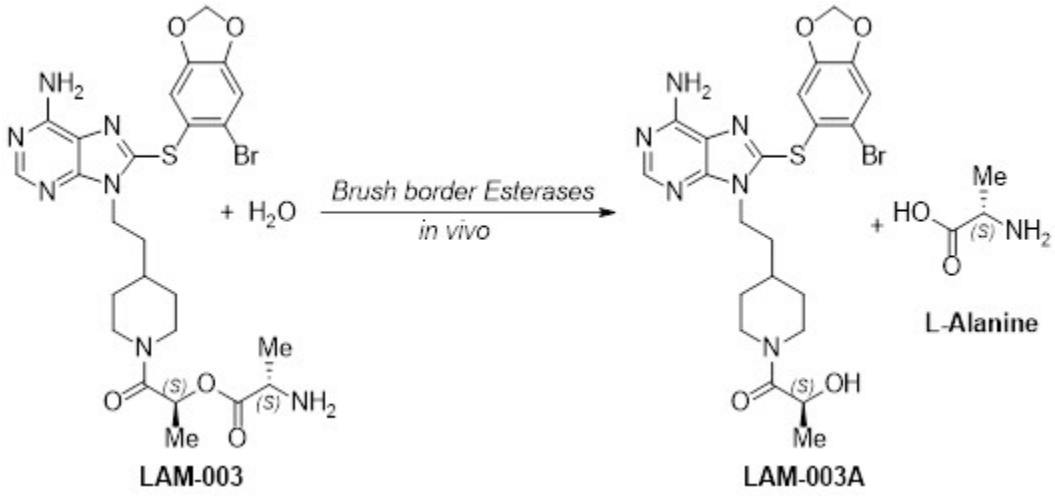
Figure 1. LAM-003 Structure



The molecular formula is $C_{25}H_{30}BrN_7O_5S \bullet CH_4O_3S \bullet H_2O$ and the molecular weight is 734.64 g/mole. LAM-003 is modestly soluble in water (350 μg/mL). The logarithm of the acid dissociation constant (pKa) is 6.91.

LAM-003 is the L-alanine prodrug of the active moiety LAM-003A. LAM-003 is converted by esterases to LAM-003A. This conversion occurs in vitro in culture media and in vivo at the brush border of the intestine as shown in Figure 2. Based on a LAM-003A molecular weight of 549.44, and assuming complete conversion, administration of LAM-003 is expected to result in delivery of ~75% of the LAM-003A that would occur with direct administration of LAM-003A.

Figure 2: In Vivo Conversion of LAM-003 to LAM-003A and L-Alanine



1.4.3 Nonclinical Experience

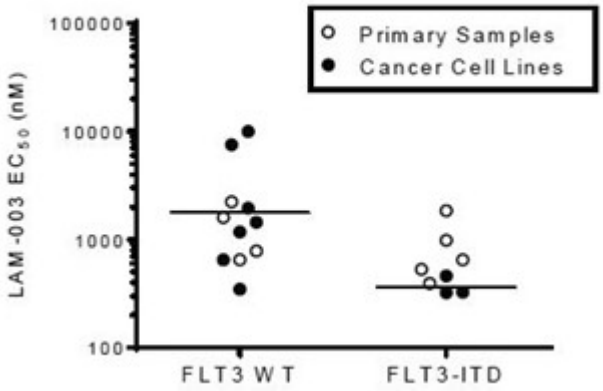
1.4.3.1 Efficacy Pharmacology

In support of clinical development, the pharmacology of LAM-003/LAM-003A has been extensively characterized in in vitro and in vivo nonclinical models of AML.

1.4.3.1.1 In Vitro Studies

In vitro studies indicated that LAM-003 demonstrates mutant FLT3 client protein degradation and preferential cytotoxicity toward AML cell lines and primary AML cells harboring a FLT3-ITD mutation (Figure 3); in these experiments, the geometric mean EC_{50} values were 576 nM for FLT3-ITD-mutant cells (n=8) vs 1525 nM for FLT3-wild-type (WT) cells (n = 11). However, as also shown in (Figure 3), multiple FLT3-WT AML cell lines and patient-derived tumors share the enhanced sensitivity to LAM-003 displayed by FLT3-ITD AML cells in vitro.

Figure 3: LAM-003 Demonstrates Potent Antileukemic Activity in AML Cells



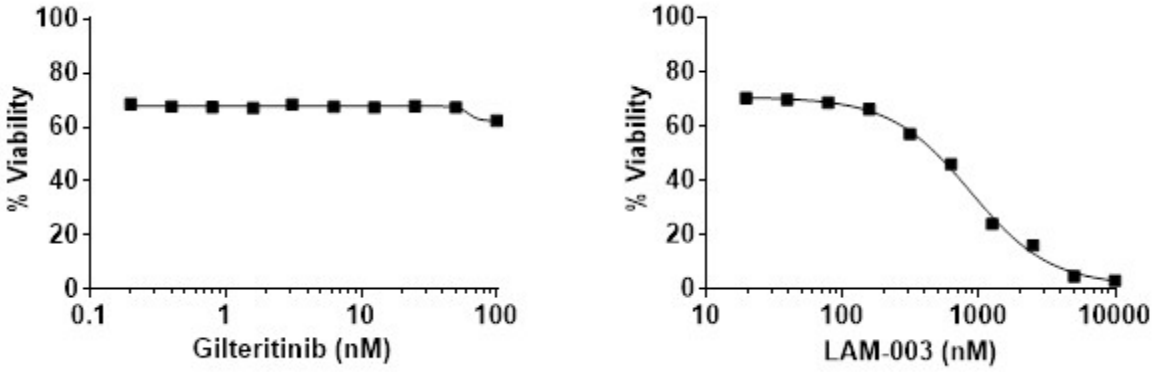
Abbreviation: AML=acute myeloid leukemia, EC_{50}=median effective concentration, FLT3=FMS-like tyrosine kinase 3, ITD=internal tandem duplication, WT=wild type

To further characterize the ability of LAM-003 to cause FLT3-mutant degradation, testing was performed on BaF3 murine cells made dependent on several oncogenic FLT3 mutations (including: FLT3-WT, FLT3-ITD, FLT3 D835V, FLT3-ITD D835V, FLT3 D835Y, FLT3-ITD D835Y, FLT3 D835H, FLT3-ITD D835H, FLT3 F691L, and FLT3-ITD F691L). As assessed by flow cytometry, LAM-003 caused similar dose-dependent reductions in FLT3 cell surface expression on all mutant cell lines but had relatively little effect on BaF3 cells expressing a FLT3-WT receptor. By this measure, FLT3-TKD mutants are as sensitive to LAM-003 degradation as FLT3-ITD mutations.

To demonstrate that LAM-003 can degrade FLT3-ITD and diminish FLT3-mediated signaling, FLT3-ITD-mutant MV-4-11 and MOLM-13 AML cells were treated with 1 μM of LAM-003 for 24 hours. Cell surface FLT3 and downstream phosphorylation of the PI3K/AKT pathway enzyme S6 were evaluated by flow cytometry. In both MV-4-11 and MOLM-13 cell lines, there was a >65% reduction in cell surface FLT3 protein and corresponding >70% reduction in phospho-S6, confirming the expected drug effects on receptor expression and function.

Importantly, LAM-003 is also active in cells that have become resistant to FLT3-ITD due to receptor mutation, upregulation of "work-around" pathways, or the influence of stromal cells that support AML survival and growth. Using the BaF3 system, LAM-003 activity was compared with that of crenolanib in a crenolanib-resistant FLT3-ITD F691L mutant. As expected, the BaF3 cells harboring the FLT3-ITD-F691L mutant displayed a 23-fold resistance to crenolanib therapy as compared with the cells harboring FLT3-ITD. In contrast, LAM-003 had similar antiproliferative activity against the 2 FLT3-ITD mutant cell lines. LAM-003 cytotoxicity was also compared in parental MOLM-13 cells, which harbor FLT3-ITD and are midostaurin-sensitive, to cytotoxicity in a MOLM-13 cell line grown in midostaurin to generate a midostaurin-resistant cell line. The MOLM-13 resistant cell line showed respective 2.5-fold and 3-fold increases in EC_{50} values relative to the sensitive line for midostaurin and crenolanib, while the increase for LAM-003 was only 1.5-fold. In addition, when MOLM-14 FLT3-ITD-mutant cells were seeded in bone-marrow-stroma-conditioned medium, the FLT3 inhibitors gilteritinib and crenolanib showed marked loss of activity (increases in EC_{50} by >15- and >30-fold); in contrast, LAM-003 retained antiproliferative activity under stromal conditions, with only a 1.6-fold increase in EC_{50}. Particularly important in support of the proposed study was an evaluation of cancer cells from a patient who had primary refractory FLT-3-mutant AML progressing after cytarabine/idarubicin induction chemotherapy, high-dose chemotherapy/total body irradiation with hematopoietic progenitor cell transplantation, gilteritinib, and sorafenib. In vitro analysis of cell viability (using Annexin V/7-AAD exclusion) confirmed resistance to gilteritinib but showed that the AML cells from this patient remained sensitive to LAM-003 (see Figure 4).

Figure 4. LAM-003 In Vitro Efficacy in Cancer Cells from a Patient with Gilteritinib- and Sorafenib-Resistant AML



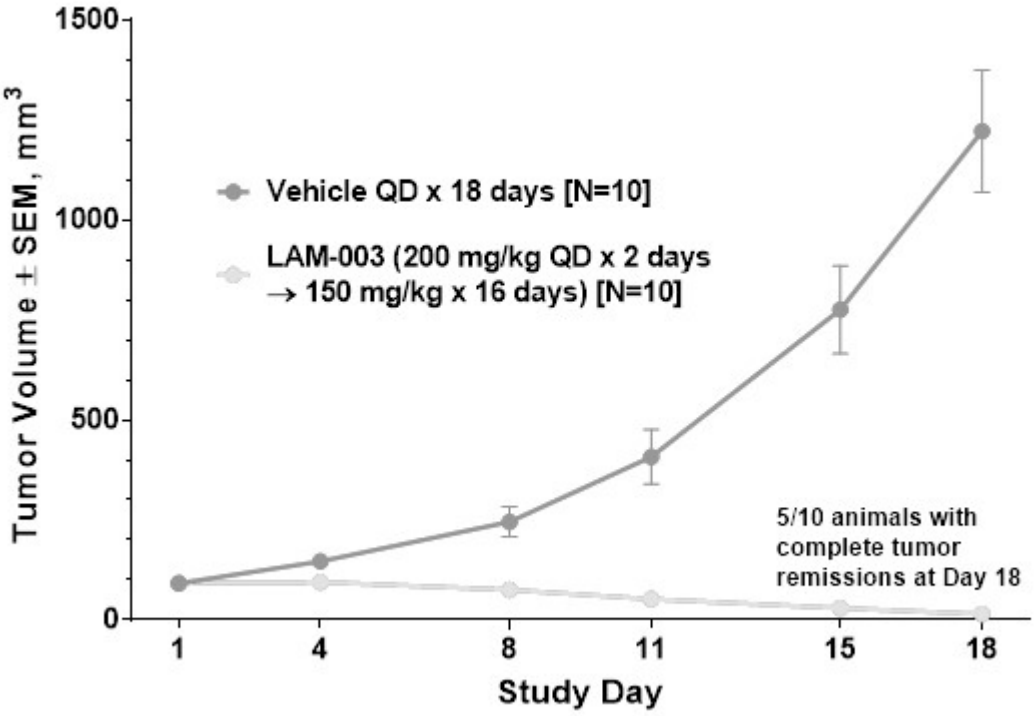
Abbreviation: AML=acute myeloid leukemia

T-cell-derived interferon gamma (IFNγ) has been shown to induce the protein expression of programmed death-ligand 1 (PD-L1) in a variety of cancer cell types, thus providing a mechanism by which tumor cells can evade immune detection. To test whether LAM-003 can block IFN-γ-induced PD-L1 expression, 6 primary AML samples (FLT3-WT, n=2; FLT3-ITD, n=4) were treated with human IFNγ alone, LAM-003 alone, or a combination of IFNγ and LAM-003 for 24 hours. At this timepoint, LAM-003 did not affect the viability of the AML blasts. Samples from all patients responded to IFNγ treatment by increasing the amount of PD-L1 on the cell surface (5- to 25-fold). LAM-003 alone did not affect basal PD-L1 cell surface protein. However, when combined with IFNγ, LAM-003 significantly reduced IFNγ-induced PD-L1 cell surface expression. These data show that, in addition to possessing cytotoxic activity against AML, LAM-003 may also possesses salutary immunopotentiating activity.

1.4.3.1.2 In Vivo Study

A xenograft study using the MV-4-11 AML cell line was performed in mice to demonstrate the in vivo efficacy of LAM-003. In animals with baseline subcutaneous tumor volumes of 80 to 120 mm^3, LAM-003 (200 mg/kg once per day [QD] × 2 days →150 mg/kg QD × 16 days), resulted in tumor regression on Day 24. Cells had regressed relative to baseline by a mean of 83.7% and relative to control animal by 99% ($p<0.001$, unpaired t-test) (see Figure 5). Particularly notable was that 5 of the 10 animals in the LAM-003 group had complete tumor regressions. Also notable was that these highly significant anti-tumor effects were achieved without adverse effects on mean animal body weights.

Figure 5. LAM-003 Efficacy in a Subcutaneous MV4-11 Human AML Xenograft Model in Immunodeficient Mice



Abbreviations: QD=once per day, SEM=standard error of the mean

1.4.3.2 Safety Pharmacology

In a Good Laboratory Practices (GLP) study evaluating the potential effects of LAM-003A on cardiac repolarization, LAM-003A concentrations of 1 and 3 µM inhibited the human ether-à-go-go-related gene (hERG) potassium current by 12% and 21%, respectively. The 50% inhibitory concentration (IC_{50}) of LAM-003A could not be determined because of solubility limitations. The results suggest minimal clinical potential for QT prolongation as predicted by this assay and when adjusting for protein binding (see Section 1.4.3.3).

The potential cardiovascular effects of LAM-003A were evaluated in vivo in female cynomolgus monkeys administered single doses of 0 (vehicle), 25, 50, and 100 mg/kg of LAM-003A by oral gavage. No biologically significant changes were observed in any hemodynamic measurement (systolic or diastolic blood pressure, mean arterial pressure, or heart rate), qualitative or quantitative electrogram (ECG) parameters, or troponin I levels after administration of any dose of LAM-003A. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 100 mg/kg (the highest dose tested).

Respiratory effects were evaluated in a single-dose study in Sprague-Dawley rats administered single doses of 0 (vehicle), 100, 200, or 350 mg/kg of LAM-003A by oral gavage. No adverse effects of any dose were observed on clinical signs, respiratory rate, tidal volume, or minute volume. Based on these results, the NOAEL was considered to be 350 mg/kg (the highest dose tested).

Acute neurobehavioral effects were evaluated in a single-dose study in Sprague-Dawley rats administered single doses of 0 (vehicle), 100, 200, or 350 mg/kg of LAM-003A by oral gavage. No adverse clinical effects were observed on any parameter of the functional observation battery (autonomic function, reactivity and sensitivity, excitability, gait and sensorimotor coordination, and grip strength) at any dose. Based on these results, the NOAEL was considered to be 350 mg/kg (the highest dose tested).

1.4.3.3 Pharmacokinetics, Metabolism, and Drug-Drug Interactions

Pharmacokinetic and toxicokinetic nonclinical studies of LAM-003 and/or LAM-003A were performed in mouse, rat, dog, and monkey species and all documented systemic exposure to the drug when administered the oral route.

Following oral administration of the LAM-003 prodrug to mice, rats, and dogs, systemic exposure to LAM-003A was equivalent to systemic exposure when LAM-003A was given directly by the oral route in equimolar doses. As anticipated, the systemic exposure to the prodrug LAM-003 was negligible.

The pharmacokinetics of LAM-003A were investigated in mice, rats, dogs and monkeys following oral and intravenous (IV) dosing. Oral bioavailability was approximately 100% for high doses in mice, ranged from 46 to 68% in rats, and 41 to 56% in cynomolgus monkeys. In toxicokinetics studies, time of maximum concentration (T_{max}) values typically ranged from 1 to 2 hours in the rat and from 2 to 3.7 hours in the monkey. Exposures increased with increasing dose across species; in monkey, increases in mean values for maximum concentration (C_{max}) and area under the concentration-time curve (AUC) appeared greater than dose proportional.

Plasma protein binding data in humans indicated that LAM-003 shows 91.6% protein binding (ie, an unbound plasma fraction of 8.4%).

There was no evidence of drug accumulation during oral dosing in the toxicokinetic studies, consistent with half-life ($t_{1/2}$) values of LAM-003A ranging from 2.6 to 13.9 hours in mice, 3.0 to 5.5 hours in rats, 3.3 to 9.4 hours in rats, and 4.5 to 9.3 hours in monkeys.

When metabolism was evaluated in human liver microsomes, 7 unique chromatographic peaks were detected by mass spectrometric-detection and the identities of 4 of these peaks were established. All metabolites detected in human microsomes were also detected in rat and/or monkey microsomes. These data confirmed that there were no unique human metabolites relative to toxicology species and that rat and monkey were appropriate species for nonclinical toxicology assessments of LAM-003A.

When evaluated in rats, the primary route of elimination for LAM-003A and metabolites appeared to be through biliary elimination. Renal elimination was negligible (<1%) in rat, dog, and monkey.

To assess for the possibility that LAM-003A metabolism might be altered by other drugs, an in vitro characterization with recombinant cytochrome P450 (CYP) enzymes was performed. This study concluded that LAM-003A was a substrate for the CYP3A4 and CYP3A5 isoforms. Until clinical drug-drug interaction data are available, these nonclinical findings suggest that coadministration of LAM-003 with strong inhibitors or inducers of CYP3A4/5 might perturb LAM-003A exposure and should be minimized (see Section 6.3.9).

The potential for LAM-003 acting as to perpetrate a drug-drug interaction was evaluated in vitro using recombinant CYP enzymes. LAM-003A did not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at concentrations that are likely to be achieved clinically. Inhibition of CYP3A4 was observed with an IC_{50} value of 0.7 μM, suggesting the possibility that LAM-003 could increase systemic exposures to drugs that are sensitive substrates of this enzyme. In a further study in pooled human liver microsomes, LAM-003A did not show direct inhibitory effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. LAM-003A did not show time-dependent inhibition potential against CYP1A2, CYP2B6, CYP2C8, CYP2C19, or CYP2D6. However, LAM-003A demonstrated some evidence of time-dependent inhibition against CYP2C9 with an IC_{50} value of 21.3 μM and more substantial time-dependent inhibition against CYP3A4/5 with IC_{50} values of 0.636 μM (midazolam probe substrate) and 0.499 μM (testosterone probe substrate). Because the prior LAM-003A Phase 1 clinical experience did not demonstrate time-dependent changes in LAM-003A C_{max} and AUC following repeated dosing, the potential for clinically significant effects of LAM-003 on drugs that are metabolized by CYP3A4 appears to be low. However, investigators are advised to use caution when administering drugs that are sensitive or low-therapeutic-index CYP3A4 substrates (see Section 6.3.9).

1.4.3.4 General Toxicology

In support of clinical development in patients with cancers, LAM-003A underwent toxicological evaluation in conformance with the International Conference on Harmonization (ICH) S9 guidance on nonclinical assessments of anticancer pharmaceuticals [FDA 2010]. This evaluation included 28-day and 16-week GLP toxicology studies in rats and monkeys that formed the central basis for Phase 1, first-in-human dose selection and clinical safety monitoring. In addition, a 28-day study compared the toxicology and toxicokinetics of LAM-003 and LAM-003A in rats.

1.4.3.4.1 28-Day LAM-003A Toxicology Study in Rats

In this GLP study, rats were administered either vehicle or LAM-003A QD by oral gavage for 28 days. Dose levels were 50, 100, or 200 mg/kg/day. The study included a 14-day recovery period.

Deaths were observed after 10 days at 200 mg/kg/day and the dose was reduced in survival animals to 100 mg/kg/day. These animals had moderate adipose tissue depletion. Ophthalmoscopic examinations were negative for all animals.

The primary effects of LAM-003A appeared to be generalized lymphoid depletion and erosion/ulcer/inflammation of the stomach; and slight changes in hematology, electrolytes, and minimal or sporadic increases in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, or sorbitol dehydrogenase. At termination, there were mild dose-dependent decreases in potassium in both sexes at all dose levels. Chloride was also mildly decreased in males at 100 mg/kg/day. Clinical findings resolved during the recovery period except for continued cell depletion of the bone marrow of some animals.

Following 28 days of oral dosing of LAM-003A in rats at dose levels of 0, 50, 100 or 200 mg/kg/day, the NOAEL was determined to be 100 mg/kg/day based on mortality noted at 200 mg/kg/day.

1.4.3.4.2 16-Week LAM-003A Toxicology Study in Rats

In this GLP study, rats were administered either vehicle or LAM-003A QD by oral gavage for 16 weeks. Dose levels were 25, 50, or 100 mg/kg/day. The study included a 4-week recovery period.

LAM-003A-related mortality occurred in males at the 100-mg/kg/day dose level (3 males in the main study and 6 toxicokinetic males). Clinical findings before death generally indicated a debilitated condition of these animals. At necropsy, the animals showed atrophy of the seminal vesicles, erosion/ulceration in the non-glandular stomach, and adipose tissue depletion in the skin and subcutaneous tissues. No other significant clinical findings were noted in this study except for decreased food consumption and body weights in animals in the 100-mg/kg/day dosing group. No ophthalmoscopic findings related to LAM-003A were observed.

Notable clinical pathology changes that were considered related to LAM-003A in males and/or females at the 100-mg/kg/day dose level included increased neutrophils in both sexes on Day 90 Serum alkaline phosphatase and gamma-glutamyltransferase (GGT) levels tended to be increased, particularly in males, on Day 90. Elevations in serum AST, ALT, and sorbitol dehydrogenase were also observed in males on Day 90 and in both sexes at termination. All changes resolved after the recovery period, and none was considered adverse.

Thymus gland weights were lower (relative and absolute) in both sexes in the 100-mg/kg/day dose group at termination. These correlated with lymphoid depletion in males. Increased adrenal weights were noted in males in the 100-mg/kg/day dose group, and decreased pituitary weights were noted in females at all LAM-003A dose levels in a dose-dependent manner. There were no microscopic correlates for the changes in adrenal or pituitary weights. All changes resolved after the recovery period, and none was considered adverse.

Microscopic changes related to LAM-003A were noted in both sexes in the 100-mg/kg/day dose group and in females in the 50-mg/kg/day dose group. These included multifocal erosions/ulcers with or without perforations (sometimes accompanied by inflammation, hemorrhage, and/or bacterial colonies) in males in the 100-mg/kg/day dose group; mixed hematopoietic cell depletion of the femur and sternum bone marrow in both sexes in the 100-mg/kg/day dose group; and generalized lymphoid depletion of the spleen with pigmented macrophages in both sexes in the 100-mg/kg/day dose group and in females in the 50-mg/kg/day dose group. Most of these findings resolved during the recovery period.

Following 16 weeks of oral dosing of LAM-003A in rats at dose levels of 0, 25, 50, or 100 mg/kg/day, the NOAEL was determined to be 50 mg/kg/day

1.4.3.4.3 28-Day LAM-003A Toxicology Study in Monkeys

In this GLP study, cynomolgus monkeys were administered either vehicle or LAM-003A QD by oral gavage for 28 days. Dose levels were 10, 25, or 50/35 mg/kg/day. The study included a 28-day recovery period.

One male and one female in the 50-mg/kg dose group were euthanized in extremis on Day 5 of dosing. Clinical signs, including soft and/or watery feces, inappetence, decreased activity, and abnormal posture, were observed in the animals in the 50-mg/kg/day dose group before death. The remaining animals in the 50-mg/kg dose group were allowed a dose holiday of 6 days and then received a reduced dose of 35 mg/kg/day for 21 days. Body weight gain was lower during the treatment period in the animals that were administered doses ≥25 mg/kg/day than in those who were administered the 10-mg/kg/day dose; weight rebounded during the recovery period. No LAM-003A-related ophthalmoscopic findings or effects on urinalysis parameters were observed.

No effect of LAM-003A was observed on qualitative ECG parameters, heart rate, PR or RR interval, or QRS duration. A mild dose-related increase in QTc interval, relative to prestudy values, was observed at the terminal intervals, but postdose values were not different from predose values. The effect on the QTc interval was reversible, and the increase in the QTc interval never exceeded 10%.

Blood samples that were collected before early termination on Day 5 from the animals in the 50-mg/kg/day dose group that had declining health status exhibited increased levels of total leukocytes (primarily neutrophils). Decreased values for erythrocytes, hemoglobin, and/or hematocrit were noted in the 25- and 50/35-mg/kg/day dose groups on Day 5 and at termination. Reticulocyte values tended to be higher than in controls on Day 5 and at termination, but the response was inadequate relative to the decreased red cell mass. Macroscopic observations included red discoloration/foci in the stomach and generalized lymphoid depletion. All these observations appeared to be reversible with cessation of treatment except for thymic depletion in 1 female in the 50/35-mg/kg/day dose group, which remained at the end of the recovery period.

Following 28 days of oral dosing of LAM-003A in monkeys at dose levels of 10, 25, or 50/35 mg/kg/day, the NOAEL was determined to be 50 mg/kg/day.

1.4.3.4.4 16-Week LAM-003A Toxicology Study in Monkeys

In this GLP study, cynomolgus monkeys were administered either vehicle or LAM-003A QD by oral gavage for 16 weeks. Dose levels were 6.25, 12.5, or 25 mg/kg/day. The study included a 4-week recovery period.

Soft/watery feces were evident in all groups, including the control group, although the incidence and severity were greater in the 25-mg/kg/day dose group than in the control group. Three animals (12.5-mg/kg/day dose group, 1 female; 25-mg/kg/day dose group, 1 male and 1 female) were euthanized in extremis secondary to the consequences of the watery/soft feces. Additional findings noted at the 25-mg/kg/day dose level included hypothermia and dehydration. Body weight gain among both sexes was lower during in the 25-mg/kg/day dose group than in the other dose groups, but this generally resolved during the recovery period. There were no ophthalmoscopic findings during the study.

No effects on qualitative or quantitative ECG parameters were observed. No adverse effects of LAM-003A were observed on any clinical pathology parameter. At necropsy, there were no organ weight effects or definitive microscopic findings that were attributable to LAM-003A.

Following 16 weeks of oral dosing of LAM-003A in monkeys at dose levels of 6.25, 12.5, or 25 mg/kg/day, the NOAEL was determined to be 12.5 mg/kg/day. The dose level of 25 mg/kg/day was considered the highest non-severely toxic dose (HNSTD) in this study.

1.4.3.4.5 Comparative Repeat-Dose Study of LAM-003 and LAM-003A

This study was conducted to evaluate the potential toxicity and toxicokinetics of LAM-003 and LAM-003A in rats when administered orally for 28 days followed by a 14-day recovery period Two groups of Sprague-Dawley rats were administered LAM-003 at dose levels of 67 and 134 mg/kg/day (respective molar equivalent doses of 50 and 100 mg/kg/day of LAM-003A). One group of animals was administered LAM-003A at a dose level of 100 mg/kg/day (the NOAEL of LAM-003A in a previous study). One additional group of animals was administered vehicle. Following 28 days of administration, recovery animals were maintained for a 14-day recovery period.

No early deaths occurred. A lower body weight gain was observed in males given 100 mg/kg/day LAM-003A and in males given 134 mg/kg/day LAM-003 during the dosing period. Further loss was not observed during recovery. No effects on food consumption or changes in ophthalmology were noted in any group.

Minimal to mild decreases in lymphocytes, eosinophils, basophils and platelets were observed in both sexes receiving 134 mg/kg/day LAM-003 and 100 mg/kg/day LAM-003A. The changes were similar in magnitude between animals receiving LAM-003 and LAM-003A. Minimal increases in serum AST and ALT were observed at termination in both sexes given 100 mg/kg/day LAM-003A. Although these changes were considered related to treatment, they were not considered biologically relevant based on their small magnitude and/or and lack of histopathologic correlates. These changes had resolved by the recovery interval.

Spleen and thymus weights were decreased in both sexes at 67 and 134 mg/kg/day of LAM-003 and at 100 mg/kg/day LAM-003A. Similar microscopic findings were observed in rats given LAM-003 or LAM-003A orally for 28 days, including minimal to mild cortical lymphoid necrosis and/or minimal to mild generalized lymphoid depletion of the thymus; minimal to mild mixed depletion of the bone marrow; and minimal edema, minimal hyperkeratosis, minimal epithelial hyperplasia and/or mild erosion/ulceration of the stomach in both sexes, primarily in the high dose groups (100 mg/kg/day equimolar dose). Minimal to moderate physeal thickening was observed in the growth plate of the femur in males in all LAM-003 and LAM-003A groups and minimal bilateral follicular cell hypertrophy in the thyroid gland was observed in females in the high-dose groups. All findings generally resolved during the recovery period. There were no toxicities observed in animals given LAM-003 that were not also observed in animals given equimolar doses of LAM-003A.

1.4.3.5 Genotoxicity

The mutagenic potential of LAM-003A was examined in the in vitro bacterial reverse gene mutation assay (Ames assay), with and without metabolic activation. LAM-003 was not mutagenic as indicated by the results of this assay.

The effects of LAM-003A were evaluated in the in vitro Chinese hamster ovary (CHO) cell chromosomal aberration assay (with and without metabolic activation). With 3 hours of treatment, LAM-003A was considered negative for inducing chromosomal aberrations without metabolic activation and showed an equivocal result due to the presence of aberrations in the cultures treated with 62.5 µg/mL with metabolic activation (but in the context of cytotoxicity and drug precipitation) With 18 hours of treatment, LAM-003A significant increases in cells with

chromosomal aberrations were observed in the cultures treated with the 2 higher concentrations of 5.0 and 15.0 µg/mL without metabolic activation.

In the in vivo bone marrow micronucleus assay, LAM-003A was assessed for potential clastogenic activity and/or disruption of the mitotic apparatus by evaluation of micronuclei in polychromatic erythrocytes. In this assay, LAM-003A was administered orally at 0, 125, 250, or 500 mg/kg to Hsd:ICR (CD-1) mice. LAM-003A did not induce statistically significant increases in micronucleated polychromatic erythrocytes in the bone marrow of the test animals. Thus, LAM-003A was considered negative for clastogenic activity as indicated by this assay.

1.4.3.6 Phototoxicity

The phototoxic potential of LAM-003 has not yet been evaluated.

1.4.3.7 Reproductive Toxicology

Twenty-eight-day and 16-week general toxicology studies in rats and monkey indicated no adverse effects of LAM-003A on female organs of reproduction. In male rats that died while receiving the high dose of 100 mg/kg in a 16-week toxicology study, atrophy of the seminal vesicles was noted, but similar effects were not described in surviving animals or those administered lower doses of LAM-003A (see Section 1.4.3.4.2). These data suggest that the risk of adverse LAM-003 effects on human fertility may be low, however, nonclinical studies have not been performed to determine specifically whether LAM-003 or its metabolites might decrease reproductive function or potential.

LAM-003 or LAM-003A has not yet been evaluated in embryo-fetal development studies. In addition, there is no information about whether the drug or its metabolites are excreted in breast milk during lactation.

Based on the information currently available, study participants will be informed of the potential for reproductive risks. Pregnant or breast-feeding women will be excluded from study participation.

1.4.4 Clinical Experience

1.4.4.1 Phase 1 Study of LAM-003A

A Phase 1, multicenter (3 centers), open-label, dose-ranging, multiple-dose study was conducted by the previous sponsor (Myrexis) to evaluate the safety and pharmacokinetics and to determine the maximum tolerated dose (MTD) of LAM-003A in patients with advanced solid tumors.

Twenty-six subjects (13 males and 13 females) of median age 63.5 years (range: 45 to 85 years) with diverse types of tumor histologies (ie, cancers of the breast, colon, lung, prostate, kidney, salivary gland; melanoma, mesothelioma, sarcoma; unknown primary) were enrolled to receive repeated 21- to 28-day cycles of LAM-003A self-administered orally on a QD or twice-per-day (BID) schedule. Dosing regimens included 50 mg/m^2 QD (n=1), 100 mg/m^2 QD (n=1), 165 mg/m^2 QD (n=1), 245 mg/m^2 QD (n=6), 340 mg/m^2 QD (n=2), 340 mg/m^2 BID (n=6), 240 mg BID (n=4), and 320 mg BID (n=5). Subjects received a mean of 1.7 cycles of therapy (range, 0 to 13 cycles).

Based on pre-established definitions of dose-limiting toxicity (DLT), an MTD was not determined. However, the drug was not well tolerated at total doses of >600 mg per day due to Grade 1-3 gastrointestinal adverse events (AEs) of nausea, vomiting, abdominal pain, diarrhea, and/or enteritis in 10/10 subjects.

Cardiovascular-related AEs were considered possibly related to the study drug in 3 subjects; these events included Grade 1 sinus tachycardia in 2 subjects in the 640-mg dose group and Grade 3 supraventricular tachycardia in 1 subject in the 245-mg/m^2 dose group. Electrocardiograms that were monitored on Days 1 and 21 for 8 to 12 hours indicated corrected QT intervals by the Fridericia correction method (QTcF) of >450 msec and ≤480 msec (Grade 1) in 4 of the 26 subjects. A prolonged QTcF interval (>500 msec) was noted in 1 subject; however, this subject had a pacemaker and the finding was not considered clinically relevant.

At doses of >600 mg per day, Grade 1-2 recoverable vision changes of light/dark adaptation difficulty, dark/dimmed vision, white ocular crescents, and/or floaters were observed in 3/10 subjects (consistent with known class effects for HSP90 inhibitors [Pacey 2011, Rajan 2011, Sessa 2013, Infante 2014, Bendell 2015, Shapiro 2015, Bendell 2016, Kong 2016]).

Other notable potentially drug-related AEs included renal failure (1 subject) and respiratory failure (1 subject).

Pharmacokinetic findings indicated median T_{max} values in the range of 1 to 3 hours. C_{max} and AUC increased in a nearly dose-proportional manner across the dose levels. Exposures were generally 1- to 2-fold greater on Day 21 than on Day 1, indicating minimal to modest drug accumulation. The average t½ based on all cohorts after repeated dosing was 11.2 hours, supporting QD or BID dosing.

1.4.4.2 Phase 1 Study of LAM-003 (Current Study)

This ongoing Phase 1 multicenter, open-label, 3+3 dose-escalation study is being conducted by AI Therapeutics to evaluate the safety and pharmacokinetics and to determine the MTD of LAM-003 in patients with previously treated, relapsed or refractory AML. As of a cut-off date of 10 Jun 2019, 9 subjects (6 males and 3 females) ranging in age from 26 to 82 years had received LAM-003 self-administered orally on a QD schedule. Dosing regimens included 200 mg QD (total n=6, DLT evaluable n=3) and 300 mg QD (total n=3, DLT evaluable n=3). Durations of LAM-003 administration at 200 mg QD were 2, 9, 12, 28, 56, and 57 days. Durations of LAM-003 administration at 300 mg QD were 21, 28, and 36 days. Reasons for discontinuation were progressive disease or lack of sufficient treatment response (n=8) or intercurrent illness due to AML complications (n=1).

AEs appeared to be primarily related to AML, comorbid medical conditions, intercurrent illness or concomitant medications. Obvious LAM-003-related toxicities were not evident and no DLTs occurred. Laboratory or ECG abnormalities clearly attributable to the study drug were not observed. No drug-related ophthalmological findings were described.

Pharmacokinetic data were available from subjects at LAM-003 dose levels of 200 mg QD (Day 1, n=4; Day 8, n=3) and 300 mg QD (Day 1, n=3; Day 8, n=3). As expected, exposure to the prodrug (LAM-003) in the systemic circulation was below the lower limit of quantitation of the assay (<1.0 ng/mL). LAM-003A exposures in the plasma was observed in all subjects. Increases in LAM-003A exposures were generally proportional to increases in LAM-003 dose. It

appeared that LAM-003A steady state was achieved between Day 1 and Day 8; LAM-003A concentrations at 24 hours following the first dose on Day 1 were comparable to trough levels on Day 8 and LAM-003A AUC values were similar on Days 1 and 8. The pharmacokinetic profile of LAM-003A following LAM-003 administration was consistent with that observed with LAM-003A administration in the prior Phase 1 experience in patients with solid tumors.

1.5 Conclusions

The conduct of this Phase 1 study of LAM-003 in patients with AML is founded on a current understanding of the natural history and current therapies for patients with this malignancy; knowledge of the importance of FLT3 and HSP90 cellular pathways in the pathophysiology of this disease; and nonclinical and clinical information regarding the efficacy and safety of LAM-003 and LAM-003A. The collective data support the following conclusions:

- Relapsed or refractory AML is a serious, disabling, and life-threatening disorder. Existing therapies can induce complete tumor regressions but often lose effectiveness over time. Through its effects as an HSP90 inhibitor and immunopotentiator, LAM-003 offers the potential for overcoming disease resistance and improving clinical outcomes for patients with previously treated AML.
- Clinical evaluation of LAM-003 in patients with AML has sound scientific rationale based on evaluation of its therapeutic potential in in vitro and in vivo models relevant to human leukemia.
- Advancing the development of LAM-003 in this study is well supported by nonclinical evaluations of LAM-003 and LAM-003A pharmacology, pharmacokinetics, and toxicology and by Phase 1 assessment of the safety and pharmacokinetics of LAM-003A in patients with solid tumors. This collective information provides a basis for subject enrollment criteria; starting dose selection and dose escalation; administration of an appropriate dosing regimen and supportive care; and for safety, pharmacodynamic, pharmacokinetic, and efficacy monitoring within this study.
- Given the seriousness of previously treated, progressive AML and the aggregate potential benefits considered in the context of potential risks, clinical development of LAM-003 in patients with AML is justified.

The rationale for specific design features of the study is provided in relevant sections of the protocol, including Section 2.3 (Rationale for Study Design), Section 4.3 (Rationale for Selection of Endpoints), Section 5.6 (Rationale for Subject Selection), and Section 6.6 (Rationale for Study Drug Administration and Supportive Care).

2 STUDY DESIGN AND CONDUCT

2.1 Study Design

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 will self-administer oral LAM-003 QD or BID continuously in repeated 28-day cycles. Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher dose levels of LAM-003 using a standard 3+3 dose-

escalation design. Based on the pattern of DLTs observed in Cycle 1, escalation will proceed to define an MTD and a recommended dosing regimen (RDR) that may be at the MTD or a lower dose within the tolerable dose range.

2.2 Study Conduct

The study will be performed in accordance with the principles as set forth under the requirements of 21 Code of Federal Regulations (CFR) 50 and the ICH E6 GCP guideline. The research will be overseen by an institutional review board/independent ethics committee (IRB/IEC). The study protocol, any protocol amendments, informed consent documents, and any material used to describe the trial to potential subjects will be reviewed and approved by the IRB/IEC prior to the performance of any study-related procedures.

AI Therapeutics, Inc. will serve as the regulatory sponsor for the study and will maintain an investigational new drug (IND) application with the FDA. The protocol will be submitted to an IND for LAM-003 (IND#112055) and the trial design and results will be subject to review by the FDA.

AI Therapeutics, Inc. will also serve as the operational coordinator of the study and will oversee conduct of the study at participating study centers and through contract research organization (CROs). The CROs will perform activities relating to medical monitoring; pharmacovigilance; site monitoring; data management and study reporting; sample handling; and centralized performance of pharmacokinetic and pharmacodynamic assays, evaluation of ECG data, and reviews of drug efficacy.

During the study, assessments of safety and trial conduct will be performed by a safety review committee (SRC) comprising the investigators and clinical representatives of the sponsor. AEs and serious adverse events (SAEs) will be reviewed on an ongoing basis to identify any safety concerns. Conference calls among the members of the SRC will be conducted periodically to discuss study progress, exchange study information, and review safety events (in particular, DLTs; SAEs; adverse events of special interest; and AEs leading to dose interruption, dose reduction, or therapy discontinuation), 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.

A central histopathological review of bone marrow and peripheral blood results will be established to evaluate changes in AML disease status. The review will be performed by a board-certified hematopathologist and will be managed by a CRO selected by the sponsor. The findings of the central review (considered together with any pertinent radiographic or clinical information regarding extramedullary disease) will be considered primary for analyses of efficacy endpoints.

2.3 Rationale for Study Design

The study has been designed to provide critical dosing, safety, pharmacokinetic, pharmacodynamic, and early efficacy data in support of future clinical development of LAM-003 in larger clinical trials.

Dose-ranging in cohorts of 3 to 6 subjects using a 3+3 design is consistent with usual oncologic drug development in the Phase 1 evaluation of various types of anticancer agents; this method provides efficient dose escalation while limiting the number of subjects who are exposed to excessively toxic doses of study drug.

Centralized conduct of the study using experienced sites, investigators, CROs and laboratories is intended to provide a consistent approach to assessments of LAM-003 safety, pharmacology, and efficacy. Establishment of an SRC ensures collective investigator and sponsor input into critical assessments and decisions affecting trial conduct. Central histopathological review of AML disease status offers a systematic expert interpretation of efficacy results.

3 STUDY OBJECTIVES

3.1 Primary Objective

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

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

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

4 STUDY ENDPOINTS

4.1 Primary Endpoints

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

4.2 Secondary Endpoints

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 treatment-emergent adverse events (TEAEs); laboratory abnormalities; vital sign/oxygen saturation abnormalities; adverse ECG findings; DLTs; SAEs; adverse events of special interest; or AEs leading to interruption, modification, or discontinuation of study treatment (referencing the Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03 [NCI 2010], for grading of the severity of AEs and laboratory abnormalities)
- Type, frequency, and timing of use of supportive care and other concomitant medications

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 plasma AUC, C_{max}, time of maximum concentration [T_{max}], volume of distribution [Vd], terminal elimination half-life [$t_{1/2}$], terminal elimination rate constant [λz], and apparent clearance [Cl/F]) (as determined using noncompartmental methods)

4.2.3 Antitumor Activity and Survival

Efficacy will be evaluated using standard remission and progression criteria [Cheson 2003, Döhner 2017] 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: 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 $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/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

4.2.4 Exploratory Endpoints

4.2.4.1 Pharmacodynamics

- Changes in 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 FL concentration (as measured using an immunoassay)
- Changes in 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)

4.2.4.2 Biomarkers

- Baseline AML blast FLT3 mutation type and FLT3 mutation-to-WT allele ratio
- Baseline mutational profile in AML blasts (with germ-line control in saliva) (as assessed with next-generation sequencing [NGS])

4.3 Rationale for Selection of Endpoints

The proposed endpoints have been chosen based on relevance to the pathophysiology and clinical manifestations of AML; the known pharmacology of LAM-003/LAM-003A; and the goals of the study in establishing an appropriate LAM-003 dosing regimen and providing information regarding its efficacy. These types of endpoints have been employed in prior studies evaluating LAM-003A or other anticancer agents and can be evaluated with acceptable accuracy and reliability.

Determination of an optimal dosing regimen is critical to ensuring adequate benefit:risk for future development. Selection of a final RDR will focus on evaluation of any DLTs in the first 4 weeks of therapy (Cycle 1) but will also seek to balance short- and long-term safety

information with treatment administration, general feasibility, pharmacology, and efficacy findings.

In defining the therapeutic ratio of a treatment for use in a clinical setting, it is imperative that its safety profile be fully characterized. Proper description of each AE or laboratory abnormality requires an understanding of the type, incidence, timing, severity, and relatedness to study drug. In this study, particular focus will be placed on monitoring for toxicities that were encountered in the nonclinical studies and prior clinical study of LAM-003A. For consistency of interpretation, AEs will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs and laboratory abnormalities will be graded using the well-defined CTCAE, Version 4.03 [NCI 2010]. Standard definitions for seriousness will be applied (see Section 8.1.2). In the evaluation of safety, particular scrutiny will be applied to Grade ≥3 AEs; to AEs causing interruption, dose modification, or discontinuation of the study drugs; and to SAEs. ECG evaluations will be performed to evaluate for any drug-related dysrhythmias, wave-form abnormalities, or perturbations of cardiac intervals; obtaining ECG data in coordination with pharmacokinetic analyses will permit exploration of exposure-QTc relationships. Ophthalmologic monitoring is consistent with recommendations for the characterization of findings in patients receiving antineoplastic agents with potential ocular toxicities [Renouf 2012], considering the potential mechanisms of HSP90 inhibitor effects on vision [Ochoa 2002, Sakai 2003, Zhou 2013, Kanamaru 2014].

Blood sampling for derivation of pharmacokinetic parameters is intended to provide characterization of LAM-003/LAM-003 exposure and disposition; evaluate for dose-exposure, pharmacokinetic-pharmacodynamic, and exposure-response relationships; assess drug accumulation with repeated dosing; and consider the implications of exposure analyses in establishing an optimal dosing regimen. Sampling is planned on Cycle 1 Day 1 (C1D1) and C1D8 (see Section 7) to generate acute and steady-state LAM-003 exposure information within a time period that will allow an assessment of LAM-003 accumulation but is sufficiently short so as to minimize loss of data due to subject dropout. On those days, frequent sampling for 8 hours postdose will provide detailed plasma concentration-time curves and permit generation of pharmacokinetic parameters while minimizing inconvenience for study participants and study center staff. Evaluation of LAM-003 plasma concentrations will be performed using liquid chromatography with tandem mass spectrometry as established in animal studies and validated for human plasma. Plasma samples will be retained for potential later analyses of LAM-003A metabolites.

Determinations of the magnitude and duration of changes in AML disease status will be based on well-established remission and progression criteria [Cheson 2003, Döhner 2017] as applied to bone marrow and peripheral blood laboratory measurements (and to radiographic or clinical information in subjects with extramedullary AML). Beyond assessing the ability of the study drug to control cancer growth, AML assessments will also be considered in defining the proper duration of treatment for each study participant. The specific endpoints of overall cancer control evaluated in this trial are customarily assessed and reported in studies of new therapies in patients with AML. CR_{MRD-}, CR, CRi, and PR provide convenient categorization of the magnitude of clinically meaningful reductions in the extent of AML. TTR, DOR, and EFS offer well-established outcome measures that directly evaluate treatment effect, convey important information regarding the rapidity and duration of clinical benefit, can be characterized in all subjects using intention-to-treat principles, and are readily analyzed using statistical methods

such as Kaplan-Meier techniques. The 8- to 12-week cadence of tumor assessments is consistent with the expected natural history of remission and progression in relapsed AML, current clinical practice, and the goals of the trial in documenting meaningful LAM-003-mediated AML regression

Changes in FLT3 expression, FLT3 pathway activation, HSP protein and gene expression, and PD-L1 expression in AML blasts are assessed during C1 therapy to provide evidence of drug mechanism, offer context for efficacy findings, and assist in final dose and schedule selection. Changes in plasma FL concentrations are intended to provide information that may corroborate drug effects on cellular alterations in FLT3. Immunophenotyping assays for changes in circulating B-cell, T-cell, NK cell, and monocyte subsets will characterize the peripheral immune status of the subject and any possible LAM-003 effects on these parameters. Baseline evaluations of FLT3 and overall mutational status in AML blasts are intended to generate subject selection hypotheses for future studies.

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS

5.1 Planned Number of Subjects

The total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all 5 planned starting dose levels and 6 additional subjects are enrolled at the MTD or RDR, as many as 36 subjects could be enrolled. If an additional dose level or an additional schedule (eg, BID) administration is explored in 6 subjects per cohort, as many as 12 additional subjects could be enrolled, bringing the potential sample size to 48 subjects. To allow for the possibility that some subjects may not be fully evaluable, up to 60 subjects may be enrolled.

5.2 Recruitment of Subjects

Subjects will be enrolled, dosed, and evaluated by study center personnel who are experienced in the conduct of studies in subjects with relapsed AML. Patients who are being followed at each study center or are referred to the study center are candidates for the study. Study center coordinators may recruit appropriate candidates for screening by study physicians. The principal investigator, designated sub-investigators, or other designees at the study center will discuss the possibility of participation directly with patients who may be appropriate candidates for the study.

Any recruitment or advertising materials will meet criteria as outlined in 21 CFR 50, “Protection of Human Subjects,” and will be approved by an IRB/IEC before implementation. These materials will not be coercive or offer undue inducements and will accurately reflect information regarding the study.

The sponsor will post a description of the study on the ClinicalTrials.gov website.

5.3 Informed Consent Process

Study candidates will be given a written informed consent document that describes study procedures, potential risks, and potential benefits, and informs them of their rights if they elect to become participants in the study. The informed consent document will be provided to them in a language that they understand well.

Prior to study candidate screening for enrollment in the study, the investigator or designee at the study center will describe the risks and benefits of participation in the study. Adequate time will be given to study candidates to read the informed consent document and to decide whether or not to participate in the study. Study candidates will be encouraged to ask questions of the study physician during the consent process and throughout the trial. They will be offered the option to take a copy of the informed consent document home to discuss the study with family, friends, and/or health care providers before deciding to take part in the study. If they agree to participate in the study, they will be required to sign and date the consent document and will be given a signed and dated copy to keep. Signing of the informed consent document by the study candidate will be required prior to initiation of any study activities that are not part of routine medical care.

5.4 Enrollment and Replacement of Study Subjects

Inclusion and exclusion criteria will be reviewed for each potential subject by qualified study center personnel. If the consented study candidate is considered eligible for study participation, the study center will transmit a study-specific eligibility and enrollment form to the sponsor (or a designee). If medically appropriate, study candidates who do not initially meet screening criteria may be rescreened with the approval of the medical monitor.

The sponsor (or a designee) will acknowledge receipt of the study candidate's eligibility form and will complete the enrollment form indicating the LAM-003 dosing regimen. The enrollment form will be transmitted to the study center. Once the study center receives the completed enrollment form, the subject can begin treatment.

Subjects who do not have the necessary baseline and on-study measurements to provide interpretable results for safety, pharmacodynamic, pharmacokinetics, or efficacy parameters may be replaced at the discretion of the SRC. In general, this will mean that subjects who do not complete study drug administration and protocol evaluation through Week 4 of therapy will be considered for replacement. The replacement subject will be assigned to the same treatment cohort as the original subject. Accrual of additional subjects to a cohort may also be considered at the discretion of the SRC. Replacement subjects or additional subjects may be accrued if there is agreement that treatment of such subjects is unlikely to constitute an unacceptable safety risk.

5.5 Subject Selection Criteria

This clinical trial can fulfill its objectives only if appropriate participants are enrolled. The protocol-specified eligibility criteria are designed to select subjects for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a study candidate. Eligibility criteria may not be waived by the investigator and conformance to the eligibility criteria will be reviewed in the case of a GCP or a regulatory authority audit. Any questions regarding a study candidate's eligibility should be discussed with the medical monitor before enrollment.

5.5.1 Inclusion Criteria

Study candidates must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Men and women of age ≥18 years.

2. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix 14.1).
3. Current diagnosis of AML.
4. AML has been previously treated and has progressed during or relapsed after prior therapy.
5. Presence of measurable AML, defined as the presence of >5% blasts in the bone marrow (based on a bone marrow sample with ≥200 nucleated cells and bone marrow spicules) and/or >1.0 × 10^9/L blasts in the peripheral blood.
6. All acute toxic effects of any prior antitumor therapy (except hydroxyurea, cytarabine, and/or cyclophosphamide given to control blast count proliferation) resolved to Grade ≤1 before the start of study therapy (with the exception of alopecia [Grade ≤2 permitted], neurotoxicity [Grade ≤2 permitted], or bone marrow parameters [Grade 1 to 4 permitted]). ***Note: For subjects with rapidly proliferative disease, use of hydroxyurea, cytarabine, and/or cyclophosphamide is allowed before the start of study therapy and during Cycle 1, but must be discontinued thereafter.***
7. Adequate hepatic profile:
   a. Serum alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN) (Grade ≤1).
   b. Serum aspartate aminotransferase (AST) ≤3 × ULN (Grade ≤1).
   c. Serum bilirubin ≤1.5 × ULN (Grade ≤ 1).
8. Adequate renal function:
   a. Serum creatinine <1.5 × ULN (Grade 1), or
   b. Estimated creatinine clearance (eCl_{CR}) >60 mL/minute (with eCl_{CR} to be calculated by the Cockcroft-Gault formula [see Appendix 14.2]).
9. Adequate coagulation profile:
   a. Prothrombin time (PT) ≤1.5 × ULN (Grade ≤1).
   b. Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (Grade ≤1).
10. Negative antiviral serology:
   a. Negative human immunodeficiency virus (HIV) antibody.
   b. Negative hepatitis B surface antigen (HBsAg) and negative hepatitis B core (HBc) antibody or undetectable hepatitis B (HBV) deoxyribonucleic acid (DNA) by quantitative polymerase chain reaction (PCR) testing.
   c. Negative hepatitis C virus (HCV) antibody or negative HCV ribonucleic acid (RNA) by quantitative PCR.
11. For female subjects of childbearing potential, a negative serum pregnancy test.

12. For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of the screening period until ≥30 days after the final dose of study therapy. ***Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional laboratory postmenopausal range and a negative serum or urine beta human chorionic gonadotropin [βHCG]); or is menopausal (age ≥50 years with amenorrhea for ≥6 months)***.
13. For male subjects who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception, willingness to use a protocol-recommended method of contraception from the start of study therapy until ≥30 days after the final dose of study therapy and to refrain from sperm donation from the start of study therapy until ≥90 days after administration of the final dose of study therapy. ***Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy***.
14. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures (including all bone marrow biopsy/aspirations and radiographic studies), and study restrictions.
15. Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

5.5.2 Exclusion Criteria

Study candidates who meet any of the following criteria will not be eligible for participation in this study:

1. Peripheral blood leukemic blast cell count >50 × 10^9/L before the start of study therapy and despite the use of hydroxyurea, cytarabine, and/or cyclophosphamide.
2. Presence of known central nervous system (CNS) leukemia. ***Note: Radiographic imaging or cerebrospinal fluid analysis is not required as a condition of enrollment into the study.***
3. Presence of another cancer with disease manifestations or therapy that could adverse effect subject safety or longevity, create the potential for drug-drug interactions, or compromise the interpretation of study results.
4. Ongoing Grade >1 proliferative or nonproliferative retinopathy (eg, due to diabetes mellitus, hypertension, macular degeneration, prematurity, genetic disorder). ***Note: Subjects with resolved retinal tears due to age-related vitreous humor shrinkage are not excluded***.
5. Significant cardiovascular disease (eg, myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure; or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.

6. Significant screening ECG abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, left bundle-branch block, 2nd-degree atrioventricular (AV) block type II, 3rd-degree AV block, Grade ≥2 bradycardia, or corrected QT (QTc by Fridericia method) >480 msec (Grade >1).
7. Gastrointestinal disease (eg, gastric or intestinal bypass surgery, pancreatic enzyme insufficiency, malabsorption syndrome, symptomatic inflammatory bowel disease, chronic diarrheal illness, bowel obstruction) that might interfere with drug absorption or with interpretation of gastrointestinal AEs.
8. Uncontrolled ongoing systemic bacterial, fungal, or viral infection (including upper respiratory tract infections) at the time of start of study therapy. ***Note: Subjects with localized fungal infections of skin or nails are not excluded. Subjects may be receiving prophylactic or therapeutic antibiotics if there is no occurrence of fever within 48 hours before starting study therapy, and if antibiotics are not proscribed due to the potential for drug-drug interactions (see Exclusion Criterion 16)***.
9. Pregnancy or breastfeeding.
10. Major surgery within 4 weeks before the start of study therapy.
11. Subject is a candidate for hematopoietic stem cell transplantation (HSCT), has an appropriate HSC donor, and is willing to undergo HSCT.
12. In subjects with prior HSCT, evidence of graft-versus-host disease (GVHD) manifesting as NCI CTCAE Version 4.03 Grade ≥2 serum bilirubin, Grade ≥3 skin involvement, or Grade ≥3 diarrhea at the start of study therapy.
13. Prior solid organ transplantation.
14. Prior HSP inhibitor therapy.
15. Ongoing immunosuppressive therapy other than corticosteroids. ***Note: At study entry, subjects may be using systemic, intraarticular, inhaled, or topical corticosteroids. During study therapy, subjects may use systemic, enteric, intraarticular, inhaled, or topical corticosteroids as required for intercurrent conditions.***
16. Use of a strong inhibitor or inducer of cytochrome P450 (CYP) 3A4 (including itraconazole, ketoconazole, posaconazole, or voriconazole) within 7 days prior to the start of study therapy or expected requirement for chronic use of a strong CYP3A4 inhibitor or inducer during Cycle 1 of study therapy (see Appendix 14.4). ***Note: For subjects requiring antifungal prophylaxis/therapy, oral fluconazole or isavuconazonium can be considered. Echinocandins (eg, caspofungin, anidulafungin, or micafungin) are also acceptable, realizing the disadvantage of the requirement for intravenous administration***.
17. Use within 7 days prior to the start of study therapy of a drug known to prolong the QT interval (see Appendix 14.5). ***Note: For subjects requiring antifungal prophylaxis/therapy, oral fluconazole is permitted given that the risk of QT prolongation is considered low (as documented in product labeling).***

18. Concurrent participation in another therapeutic or imaging clinical trial. ***Note: Subjects are not precluded from undergoing evaluations involving observation, noninvasive diagnostic procedures or sampling, or questionnaires as follow-up to a prior study or as components of a concurrent noninterventional study.***
19. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a subject's ability to provide informed consent, adversely affect the subject's ability to cooperate and participate in the study, or compromise the interpretation of study results.

5.6 Rationale for Subject Selection

In general, the eligibility criteria are designed to maximize the likelihood that study participation is appropriately matched to disease risk. The criteria limit enrollment to subjects who have incurable advanced AML, are appropriate candidates for a Phase 1 investigational therapy, are likely to tolerate study procedures, and will provide interpretable results. Investigators are requested to make appropriate judgements as to whether study enrollment is suitable for a subject considering an integrated assessment of disease status, medical condition, prior therapies, comorbidities, and other relevant factors in determining eligibility or ineligibility.

The requirement that study candidates be adults largely limits participation to subjects who can consent on their own behalf. The lack of an upper bound on the age range permits enrollment of subjects across the full spectrum of ages for which therapy with LAM-003 might be applicable. To ensure that subjects are able to perform basic self-care, they must have ECOG performance scores of 0, 1, or 2.

The requirement for the presence of AML that is measurable ensures that subjects have disease that can be fully assessed for evidence of drug efficacy.

Based on the nonclinical and clinical profile of LAM-003, subjects must not have serious prior or ongoing organ dysfunction, comorbidities, or comedication use that would compromise safety, compliance, or evaluation; such factors might mask, exacerbate, or confound the interpretation of the safety, pharmacokinetic, or efficacy profiles of study therapy. Baseline clinical safety laboratory studies are intended to ensure that subjects have adequate organ function for study participation. Screening tests such as serum virology assays are performed to exclude subjects who might be at increased risk for adverse hepatic effects or immunological effects. Pregnancy testing and restrictions on eligibility relating to reproduction, pregnancy, and nursing are important because there is no knowledge regarding the potential for LAM-003 to have adverse effects on conception, fetal development, or the health of a breast-feeding infant.

Exclusion of subjects who have undergone prior HSP inhibitor therapy is intended to avoid enrolling subjects with AML that is likely to be resistant to LAM-003. Avoidance of concomitant immunosuppressives at baseline minimizes the potential that such therapy would depress the potential immunotherapeutic effects of LAM-003 or confound adequate profiling of the LAM-003 safety profile. Restrictions on concomitant administration of CYP3A4 inhibitors are important because in vitro data suggest that LAM-003A is primarily metabolized by CYP3A4 (see Section 1.4.3.3). Exclusions for cardiac waveform or rhythm abnormalities are intended to ensure that subjects do not have conduction system disorders that would increase risk or confound on-study ECG evaluations.

To minimize missing data and premature discontinuations, subjects should have sufficient psychological and social resources to comply with study procedures and restrictions. Consistent with GCP guidelines, subjects must provide informed consent before initiation of any study procedures that are not part of routine medical care.

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT

6.1 LAM-003

6.1.1 Description

LAM-003 is formulated in white, 0.25", round, convex, film-coated tablets containing 50 mg of drug substance. Inactive ingredients include: microcrystalline cellulose, lactose monohydrate, crospovidone, hydroxypropyl cellulose, colloidal silicon dioxide, sodium starch glycolate, compritol 888 ATO, Opadry clear and Opadry white. Flaking of the non-functional surface coating may be observed on some tablets, but does not affect tablet safety, quality, purity, or potency.

6.1.2 Source

LAM-003 will be provided by the study sponsor.

6.1.3 Packaging and Labelling

LAM-003 tablets are supplied in high density polyethylene (HDPE) bottles, each of which is closed with a child-resistant, tamper-evident plastic screw cap. Each bottle contains 28 tablets and includes a silica gel desiccant packet.

Labels for LAM-003 bottles meet all applicable requirements of the Food and Drug Administration (FDA) and/or other local regulations, as applicable.

6.1.4 Shipping, Storage, and Stability

During shipping study drug bottles should remain refrigerated at temperatures of 2 to 8°C [35.6 to 46.4°F]).

LAM-003 tablets should be stored at refrigerated temperatures of 2 to 8°C [35.6 to 46.4°F]) in the bottles in which they are supplied. Desiccant packets should be retained in opened bottles and bottles should remain closed when not in use to avoid absorption by the tablets of moisture from the air. To maximize product stability, subjects should be instructed to leave the desiccant packets in the bottles and to use the entire contents of one bottle before opening another bottle.

The study sponsor will provide study centers with initial and updated product stability data, when available.

6.1.5 Dispensing

A pharmacist or other qualified staff member will dispense bottles containing LAM-003 tablets. Sufficient bottles will be dispensed to the subject to provide an adequate drug supply until the subject's next planned clinic visit at which drug will be dispensed (generally at 28-day intervals). If it is anticipated that a subject may have a potential delay in returning to the study center (eg,

due to a holiday), an additional bottle may be provided at the start of therapy so that the subject has an overage supply to cover any potential delays in returning to the study center. Sites should take care to minimize waste.

For LAM-003 doses that are taken in the study center, subjects will take the dose from the drug dispensed to them for that specific dispensing interval. All other LAM-003 doses will be taken at home.

6.1.6 Return and Compliance Assessment

At the completion of each dispensing interval, empty, partially used, or full bottles of LAM-003 should be retrieved from the subject. The quantities of unused LAM-003 and the date when these study supplies are returned by the subject should be recorded in the study drug accountability records. In addition, the subject's dosing diary should be reviewed at each visit, any incomplete or inconsistent entries should be addressed, and the dosing diary should be photocopied. Returned bottles may be redispensed to the same subject but not to another subject. Returned tablets and bottles may be destroyed according to the site's standard operating procedures (see Section 12.11).

6.1.7 Accountability

See Section 12.11 for information regarding LAM-003 drug accountability.

6.1.8 Overdose Precautions

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the overdose limit. In the case of a discrepancy in drug accountability, an overdose will be established only when it is clear that the subject has received an excess dose or the investigator has reason to suspect that the subject has received an excess dose.

There are limited data on the effects of LAM-003 overdose. LAM-003A doses as high as 320 mg BID (640 mg QD) were achieved in a prior Phase 1 study.

For this protocol, an overdose of LAM-003 is defined as administration of a daily dose ≥50 mg above the prescribed dose. In a subject who experiences an overdose, consideration should be given as to whether LAM-003 administration should be temporarily interrupted. If the overdose is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and safety laboratory parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management should be instituted to mitigate adverse effects. The subject should remain under observation until adverse effects have recovered to baseline. There is no specific antidote for LAM-003.

The medical monitor should be contacted if a study drug overdose occurs. The occurrence of an overdose does not preclude further protocol therapy if the subject appears to be safely benefiting from treatment and the circumstances that led to the initial overdose are unlikely to recur.

6.1.9 Inadvertent Exposure Precautions

Based on available data, LAM-003 is not expected to be acutely toxic, irritating, or genotoxic at levels that are likely to result from inadvertent exposure. However, personnel handling the drug

should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of LAM-003. Subjects should be instructed to keep the drug secured such that it is out of the reach of children and is not inadvertently taken by others. The LAM-003 investigator brochure can be consulted for further information regarding exposure and spill precautions.

6.2 Study Drug Administration

6.2.1 Premedications

6.2.1.1 Antidiarrheal or Antiemetics

Prophylactic administration of antidiarrheals or antiemetics on or before C1D1 should be avoided unless the emerging safety profile of the study drug indicates that initial antidiarrheal or antiemetic prophylaxis is warranted. On other days, antidiarrheals and/or antiemetics may be given to minimize any potential study-drug-related nausea (see Section 6.3.5 and Section 6.3.6).

6.2.1.2 Tumor Lysis Syndrome (TLS) Prophylaxis

The general risk for TLS can be characterized according to the following criteria, considering established algorithms relevant to AML [Cairo 2010, MDACC 2013, Ejaz 2015]:

- Low risk: Serum lactate dehydrogenase (LDH) <2 × ULN, serum uric acid <5.5 mg/dL, and WBC <25 × 10^9/L.
- Intermediate risk: Serum LDH ≥2 × ULN, or serum uric acid ≥5.5 mg/dL and <7 mg/dL, or WBC ≥25 × 10^9/L to <100 × 10^9/L.
- High risk: Serum uric acid ≥7 mg/dL or WBC ≥100 × 10^9/L.

If TLS is observed during study conduct, subjects who are at intermediate or high risk of TLS should receive medical prophylaxis according to the following prophylaxis regimen or an institutional regimen customarily used at the study center:

- Intermediate Risk: These subjects should receive allopurinol, 100 to 300 mg orally every 8 hours starting ≥24 to 48 hours before the start of study drug therapy; of note, the maximum daily allopurinol dose is 800 mg, doses ≤300 mg need not be divided, and doses should be reduced by ≥50% in subjects with renal insufficiency. In addition, subjects with hyperuricemia may receive rasburicase, 3 to 4.5 mg by IV infusion.
- High Risk: These subjects should receive allopurinol, 100 to 300 mg orally every 8 hours starting ≥24 to 48 hours before the start of study drug therapy; of note, the maximum daily allopurinol dose is 800 mg, doses ≤300 mg need not be divided (but may be insufficient for high-risk subjects), and doses should be reduced by ≥50% in subjects with renal insufficiency. In addition, high-risk subjects may receive rasburicase, 3 to 4.5 mg by IV infusion, administered 3 to 4 hours prior to the first dose of study drug.

Subjects must be monitored for TLS during C1D1 through C1D5 with assessments of vital signs, AEs, and serum chemistry and hematology laboratory studies as described in Section 7. Study centers may wish to provide additional hydration and in-patient monitoring for TLS, particularly in subjects who are at high risk.

Other information regarding the management of TLS is provided in Section 6.3.14.

6.2.2 LAM-003 Administration

In each 28-day cycle, subjects are to self-administer LAM-003 starting on Day 1 and then continuously thereafter (28 total doses/cycle). Subjects should take the study drug at approximately the same time each day, ideally at ~24-hour intervals (eg, ~8AM every day) for the planned QD schedule or at 12-hour intervals (eg, ~8AM and ~8PM every day) if a BID schedule is evaluated. In conjunction with frequent pharmacokinetic assessments on C1D1, C1D2, and C1D8, subjects should take the drug at the study center under the supervision of study personnel and the timing of LAM-003 administration must be documented in the clinic notes and/or in the subject diary. On C1D2, C1D3, C1D4, and C1D5, LAM-003 is to be administered in the study center and only after the serum chemistry results from that day have been evaluated to exclude Grade 4 TLS or Grade 3 TLS associated with Grade ≥2 renal dysfunction or other Grade ≥2 end-organ injury. While variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

At each dose administration, the number of LAM-003 tablets corresponding to the appropriate doses of each drug should be swallowed whole with 100 to 200 mL (~4 to 8 ounces) of water. Subjects should be instructed not to bite or chew the tablets. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.

In conjunction with frequent pharmacokinetic assessments on C1D1, C1D2, and C1D8, subjects should ingest the drug while fasting (defined as no food with the exception of clear liquids for ≥2 hours before and ≥1 hour after dosing). Pending the evaluation of the effect of food on LAM-003 absorption, subjects are encouraged to take the drug while fasting on other days.

6.2.3 Dose Schedule Interruptions and Vomited Doses

For the QD schedule, subjects who have a delay in administration of <12 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of ≥12 hours, the dose should not be taken. The planned timing of subsequent drug administration should not be altered.

If a BID schedule is evaluated, subjects who have a delay in administration of <6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of ≥6 hours, the dose should not be taken. The planned timing of subsequent drug administration should not be altered.

For subjects who vomit shortly after taking the study drugs, the vomited dose should not be replaced. The planned timing of subsequent drug administration should not be altered.

6.2.4 Starting Dose Levels and Dose Escalation

Cohorts of 3 to 6 subjects will be 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 will be 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 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

Abbreviations: QD=once per day

The following dose-escalation rules will be employed, considering DLTs observed in Cycle 1 of therapy:

- Each dose level cohort will initially enroll 3 subjects.
- If 0 of the first 3 subjects has a DLT, the next cohort of 3 subjects will be treated at the next higher dose level.
- If 1 of the first 3 subjects in a cohort experiences a DLT, an additional 3 subjects will be treated at that same dose level. If 0 of the additional 3 subjects experience a DLT, the next cohort of 3 subjects will be treated at the next higher dose level.
- If ≥2 of 3 or ≥2 of 6 subjects experience a DLT, the MTD will have been exceeded and 3 more subjects will be treated at the next lower dose level (if only 3 subjects were previously treated at that prior dose level). If 6 subjects were previously treated at the prior dose level, that prior dose level will provisionally be considered the MTD.
- An additional 6 subjects (up to 12 total) may be enrolled at the MTD or RDR.
- With the concurrence of the SRC, additional subjects (up to 12 subjects per dose level) may be accrued at dose levels at or below the MTD to refine the estimation of the RDR and further define the pharmacology of LAM-003. Such accrual may occur:
  - At Dose Level -1 or -2 (100 or 50 mg of LAM-003, respectively).
  - At an initially planned dose level (as indicated in Table 1) or at a dose level that lies between the initially planned dose levels.
  - Using an alternative schedule (eg, BID) with a total daily dose that does not exceed the total daily MTD (rounded up or down to the nearest even multiple of 50 mg).

The following additional procedures will be followed during the dose escalation:

- The first subject to be treated at Dose Level 1 will be observed for ≥1 week after initiation of LAM-003 before any subsequent subjects are treated at the same dose level.
- Each group of 3 subjects within a cohort must receive ≥75% (21/28 doses for a QD schedule or 42/56 doses for a BID schedule) of planned Cycle 1 LAM-003 doses per subject and must be observed for a minimum period of ~4 weeks without DLT before subsequent subjects are enrolled at the next higher dose level. Any subject without DLT who does not complete these requirements may be replaced.

- Escalation to the next dose level can only occur upon review of the available safety data from all ongoing and previous subjects and with the concurrence of the SRC.
- Intrasubject dose escalation above the initially assigned dose level will be permitted as defined in Section 6.2.7 below.
- Accrual of additional subjects to a treatment cohort may be considered by the SRC with the concurrence of the study sponsor.

6.2.5 Definition of DLTs

When each cohort has completed Cycle 1, the SRC will review safety and may review any available pharmacokinetic or pharmacodynamic data. The sponsor, working in consultation with the SRC, will determine whether a TEAE meets a definition of DLT as defined in the protocol. Reference will be made to the CTCAE, Version 4.03 [NCI 2010], for grading the severity of TEAEs, treatment-emergent laboratory abnormalities, and DLTs, considering the known safety profiles of the study drug and other medical factors.

The existing clinical experience indicates that nausea, vomiting, diarrhea, tachycardias, respiratory distress, and visual disturbances can occur in association with LAM-003A administration and may be dose-limiting at total daily doses >600 mg. Visual symptoms observed with LAM-003A have included darkening or dimming of vision, difficulties with light/dark adaptation, appearance of intermittent bilateral white ocular crescents, and visual floaters. Dose-dependent ocular symptoms described with other HSP90 inhibitors have included visual dimming, difficulties with light/dark adaptation, nyctalopia (night blindness), photopsia (perceived flashes of light), photophobia (light sensitivity), and blurred vision [Pacey 2011, Rajan 2011, Sessa 2013, Infante 2014, Bendell 2015, Shapiro 2015, Bendell 2016, Kong 2016].

Based on this information but considering the limited experience with LAM-003/LAM-003A, DLTs for the purposes of establishing the MTD and RDR in this study will be defined as any of the following TEAEs occurring in Cycle 1 of LAM-003 therapy that cannot be considered incontrovertibly related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication:

- Grade 4 neutropenia persisting for ≥28 days
- Grade ≥3 vomiting despite recommended antiemetic support
- Grade ≥3 diarrhea despite recommended antidiarrheal support
- Grade ≥2 visual disturbances
- Grade ≥2 heart failure or ventricular dysfunction
- Grade 3 TLS despite adequate prophylaxis (unless TLS results in no Grade ≥2 renal dysfunction or other Grade ≥2 end-organ injury and resolves ≤7 days from onset)
- Grade 4 TLS despite adequate prophylaxis
- Other Grade ≥3 nonhematological AEs (with the exception of asymptomatic Grade ≥3 laboratory abnormalities that improve to Grade ≤2 within 72 hours)

- The occurrence of either of the following circumstances during Cycle 1:
  - Inability to comply with ≥75% (21/28 doses for a QD schedule or 42/56 dose for a BID schedule) of planned LAM-003 doses due to an AE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication
  - Following a dose interruption starting in Cycle 1, failure to recover to baseline within 2 weeks from the last dose of LAM-003 due to a TEAE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication; occurrence of such a TEAE should also result in permanent discontinuation of study drug (see Section 6.5)

6.2.6 Definitions of MTD and RDR

The MTD is the highest tested dose level at which ≥6 subjects have been treated and which is associated with a Cycle 1 DLT in ≤17% of the subjects. The RDR may be the MTD or may be a lower dose within the tolerable dose range. Selection of the RDR will be based on consideration of short- and long-term safety information together with available pharmacokinetic, pharmacodynamic, and efficacy data.

6.2.7 Dose Modification Recommendations

If a subject experiences an AE that is suspected to be related to the study drug, appropriate monitoring and supportive care (eg, antiemetics, antidiarrheals, therapy for TLS) should be instituted consistent with the nature of the event.

If a subject experiences a Grade 4 toxicity (other than Grade 4 TLS recovering with no adverse sequalae), then the study drug administration should be permanently discontinued. If a subject experiences a DLT or a less severe AE that the investigator believes warrants dose modification, then the study drug administration should be interrupted until the toxicity recovers to Grade ≤1 or baseline. In addition, subjects who develop treatment-emergent dose-limiting visual symptoms should undergo more frequent ophthalmological consultation (eg, at ~2-week intervals or more frequently, as appropriate) (see Section 6.3.13). If the drug is resumed after a dosing interruption, the dose of LAM-003 should be reduced by 1 dose level (reference Table 1). Two successive adjustments to progressively lower dose levels can be made. If the subject cannot tolerate LAM-003 after a decrease in dose by 2 dose levels or to Dose Level -2 (50 mg/day), then the subject should be discontinued from study drug therapy.

In general, after the LAM-003 dose is reduced, the dose should be maintained at that dose level, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of LAM-003 for ≥4 weeks with no toxicities of Grade ≥2, then the LAM-003 dosing regimen may be reescalated to the next higher dose level if the AE that prompted the dose reduction comprised TLS or if further evaluation reveals that the AE that led to the dose reduction was incontrovertibly related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication. Successive adjustments to progressively higher dose levels can be made. However, during the first 2 cycles of therapy, the escalated dose cannot exceed the starting dose level for that subject.

Individual subjects may have the LAM-003 dose escalated to the next higher dose level after ≥1 cycle of therapy if both the principal investigator and the medical monitor agree that the subject is tolerating the current dose level with no toxicities of Grade ≥2 and that a dose escalation is medically warranted to try to obtain better disease control (eg, for a subject who has not shown an improvement in AML disease burden by the end of the cycle). In such subjects, successive adjustments to progressively higher dose levels can be made at intervals of ≥4 weeks with the caveat that the escalated dose cannot exceed 750 mg QD (highest plan dose level) or the established MTD (if lower). As directed by the medical monitor, certain safety and other studies (eg, serum chemistry, hematology, ECG, ophthalmology, pharmacokinetic, and pharmacodynamic evaluations) may be repeated at the higher dose level per the Cycle 1 schedule for these tests.

In a subject who experiences an AE precluding resumption of LAM-003 therapy by Day 29 of the current cycle (planned Day 1 of the next cycle), the new cycle of treatment may only begin when AEs or laboratory abnormalities have returned to baseline levels and if the subject does not meet criteria for permanent discontinuation of study therapy (see Section 6.5). Upon initiation of a new cycle, the current cycle will be considered completed.

Investigators are requested to discuss modifications in the dosing regimen with the medical monitor. The appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level.

6.3 Supportive Care

6.3.1 General Recommendations

Consistent with subject safety and comfort, administration of any prescription or over-the-counter drug products other than study medication will be minimized during the study period. Subjects should be discouraged from use of herbal remedies, self-prescribed drugs, tobacco products, or street drugs during their participation in the clinical study and should be counseled to minimize use of alcohol or nonmedical marijuana.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator's decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise interpretation of study endpoints.

Subjects will be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the study.

Recommendations regarding specific types of concomitant therapies, supportive care, diet, and other interventions are provided below. To minimize variations in supportive care, the recommended supportive care agents should be considered unless there is a medical rationale in a specific subject for use of an alternative product.

6.3.2 Antibiotics, Antifungals, and Antivirals

Local practices or guidelines regarding infection prophylaxis may be followed. Subjects developing an intercurrent infection during study drug treatment may receive therapeutic antibacterial, antiviral, or antifungal drugs as needed. However, care should be taken to avoid or minimize concomitant administration of prophylactic or therapeutic antibacterial, antifungal, or antiviral, agents that are strong CYP3A4 inhibitors or inducers (see Section 6.3.9 and Appendix 14.4). Continuation of study therapy during treatment for an intercurrent infection is at the discretion of the investigator.

6.3.3 Anticancer Therapies Other than the Study Drugs

Other than hydroxyurea, cytarabine, and/or cyclophosphamide used during Cycle 1 to control AML blast counts, no systemic anticancer therapies (including chemotherapy, antibody therapy, hormonal therapy, immunotherapy, radiotherapy, or other experimental therapies) for the subject's cancer are permitted while the subject is receiving study treatment. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

6.3.4 Anticoagulants

As a precaution, subjects are required to have normal coagulation parameters before enrolling in this study. Use of local anticoagulation or antithrombotic agents to maintain a venous access catheter is permitted. In addition, subjects who develop conditions that require anticoagulant therapy are permitted to receive such drugs and are not required to discontinue study participation if they appear to be safely benefiting from study therapy.

6.3.5 Antidiarrheals

Subjects experiencing diarrhea (and/or abdominal cramping) may take loperamide at the earliest sign of a loose stool, an increase in bowel movements by 1 to 2 episodes compared to baseline, or an increase in stool volume or liquidity. The recommended regimen is 4 mg at the first onset of diarrhea, then 2 mg with each succeeding diarrheal stool until the subject is diarrhea-free for at least 12 hours.

Additional antidiarrheal measures may be implemented at the discretion of the investigator. Subjects should also be instructed to maintain oral fluid intake to help sustain fluid and electrolyte balance during episodes of diarrhea.

6.3.6 Antiemetics

While prophylactic antiemetics can be considered, it is preferred that antiemetics not be given prophylactically before initial study drug administration on C1D1.

If antiemetics are needed, it is recommended that subjects be offered 1 to 2 mg of the serotonin antagonist, granisetron (Kytril®, Granisol®), as an oral tablet or solution every 6 to 8 hours as needed. If subjects have persistent nausea or vomiting, consideration can be given to a 10-mg subcutaneous injection of the extended release form of granisetron (Sustol®). Alternatively, application of a 31.3-mg granisetron transdermal patch (Sancuso®) every 3 to 7 days can be considered. For transdermal prophylaxis, 24 to 48 hours may be necessary to allow a sufficient period to achieve effective granisetron systemic concentrations. Use of the serotonin antagonists, ondansetron (Zofran®, Zuplenz®) or dolasetron (Anzemet®), is discouraged before C2 due to

the possibility that such agents could prolong the cardiac QT interval during Cycle 1 ECG assessments.

The dopamine antagonist, olanzapine (Zyprexa®), at doses of 2.5 to 10 mg, may be considered alone or in conjunction with serotonin antagonists or other types of antiemetic agents. Doses of 10 mg may be sedating, which could be helpful for certain subjects, but may represent a concern for others, particularly for those who are elderly.

Based on currently available information regarding LAM-003 metabolism, the neurokinin 1 receptor antagonist, rolapitant (Varubi®), can be considered together with other anti-emetic agents, but aprepitant (Emend®) or netupitant+palonosetron (Akynzeo®) should be avoided because these drugs may inhibit CYP3A4 activity.

Benzodiazepines may be considered if such drugs do not pose risks of QT prolongation during Cycle 1 or drug-drug interactions.

Corticosteroids can be introduced if other types of antiemetic agents are not sufficiently effective.

6.3.7 Antihistamine, Antiinflammatory, or Antipyretic, Drugs

Antihistamines (eg, cetirizine, diphenhydramine), and antiinflammatory/antipyretic drugs (eg, acetaminophen [paracetamol], nonsteroidal anti-inflammatory drugs [NSAIDs]), may be used during the study, as medically warranted.

6.3.8 Corticosteroids

At study entry, subjects may be using systemic, intraarticular, inhaled, or topical corticosteroids. During study therapy, subjects may use systemic, intraarticular, enteric, inhaled, or topical corticosteroids as required for intercurrent conditions.

6.3.9 Drugs with Drug-Drug Interaction Potential

In vitro experiments indicate that LAM-003A can inhibit CYP3A4. While no clinical drug-drug interaction data are available, these nonclinical data suggest that LAM-003 could increase exposure to drugs that undergo metabolism via CYP3A4, potentially resulting in exaggerated pharmacological or toxic responses to such drugs.

A list of substrates of CYP3A4 is provided in Appendix 14.3. During study participation, coadministration of LAM-003 and any of the listed drugs should be minimized to the extent possible, particularly for drugs that are sensitive substrates of CYP3A4 or have low therapeutic indices. If medically appropriate, subjects receiving the listed drugs should have therapeutically equivalent drugs substituted, when available. If a subject develops a condition that requires use of a CYP3A4 substrate, investigators should evaluate for toxicity due to the coadministered drug and modify the dosage of that drug, as appropriate.

While clinical data are not yet available, in vitro data suggest that LAM-003 is metabolized by CYP3A. Based on these findings, protocol candidates who require therapy with the strong CYP3A4 inhibitors or inducers listed in Appendix 14.4 should not be enrolled into the study. If medically justified, protocol candidates may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not strongly affect this enzyme can be substituted >7 days before initiation of LAM-003.

During study participation, coadministration of LAM-003 with the strong CYP3A4 inhibitors or inducers listed in Appendix 14.4 should be avoided, if possible. However, a subject who develops a condition that may require use of such drugs is not required to permanently discontinue LAM-003 if the subject is experiencing clinical benefit and other options for treating the subject's cancer are limited. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to affect these enzymes.

For subjects who require temporary use of a drug that does affect these enzymes (eg, treatment with a systemic antifungal agent), LAM-003 therapy can be temporarily interrupted and then resumed after completion of the other drug. For subjects who require initiation of chronic therapy with a drug that strongly affects these enzymes, investigators must consult with the medical monitor to consider the best course of action. If subjects do receive a CYP3A4 inhibitor concomitantly with LAM-003, they should be monitored closely for signs of LAM-003 toxicity. Based on consultation with the medical monitor, such subjects may be required to undergo additional pharmacokinetic testing and may require a LAM-003 dose modification.

6.3.10 Drugs Known to Prolong the QT Interval

Available nonclinical and clinical data do not suggest a high risk that LAM-003 will alter the QT interval. However, data are limited and, as a precaution, the clinical potential of LAM-003 to prolong the QT interval will be assessed in this study. Accordingly, co-administration of LAM-003 and known QT-prolonging drugs is to be minimized during Cycle 1 because use of such drugs might confound interpretation of QT data from the trial.

Based on these considerations, protocol candidates who require therapy with drugs known to prolong the QT interval (as listed in Appendix 14.5) should not be enrolled into the study. If medically justified, protocol candidates may be enrolled if such drugs are unlikely to result in QT prolongation in the specific study subject (as judged by the medical monitor), can be discontinued, or alternative drugs that do not affect QT can be substituted >7 days before the first dose of LAM-003.

After the subject is enrolled to the protocol and has been monitored for 24 hours after receiving the first dose of LAM-003, there is no specific restriction on use of drugs (eg, antiemetics) that might prolong QT interval; however, use of such drugs should be minimized.

6.3.11 Hematopoietic Support

LAM-003 is not expected to cause myelosuppression based on nonclinical and clinical experience with LAM-003A. However, subjects may experience hematological AEs related to the underlying AML or prior therapy.

Granulocyte colony-stimulating factor (G-CSF) (eg, filgrastim, filgrastim-snd, peg-filgrastim, lenograstim) or granulocyte-macrophage colony-stimulating factor (GM-CSF) (eg, sargramostim) may be administered in response to neutropenic complications, as appropriate and consistent with current guidelines [NCCN 2017a, NCCN 2017c].

Use of erythropoietic agents (eg, erythropoietin or darbepoetin) is not recommended based on current guidelines [NCCN 2017b].

Red blood cell or platelet transfusions may be administered as medically indicated.

6.3.12 Immunization

For subjects who are at risk of an infection (eg, influenza, herpes zoster) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy.

Whether the study drug would increase the risk of live viral vaccines during study therapy is unknown. Pending the acquisition of additional information, live viral vaccination during study therapy should be avoided.

6.3.13 Ophthalmological Symptom Management

Grade 1 and 2 visual disturbances are an expected effect of HSP90 inhibitor administration. Known ocular symptoms described with LAM-003A and other HSP90 inhibitors have included visual dimming, difficulties with light/dark adaptation, nyctalopia (night blindness), photopsia (perceived flashes of light), photophobia (light sensitivity), and blurred vision [Pacey 2011, Rajan 2011, Sessa 2013, Infante 2014, Bendell 2015, Shapiro 2015, Bendell 2016, Kong 2016]. These effects are likely an on-target consequence of HSP90 inhibition in the retina [Zhou 2013, Kanamaru 2014] based on a physiological role for this protein in retinal function under normal and stressed conditions [Ochoa 2002, Sakai 2003].

During the study, subjects will undergo screening and periodic ophthalmological examinations (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography) according to the schedule of activities provided in Section 7. As noted in Section 6.2.7, subjects who develop treatment-emergent dose-limiting visual symptoms should have drug interrupted and should undergo more frequent ophthalmological consultation (eg, at ~2-week intervals or more frequently, as appropriate). Symptoms should resolve to Grade ≤1 before resumption of study drug and study drug should only be resumed if such resolution occurs within 2 weeks of interruption of study drug and the subject appears to be otherwise safely benefiting from study therapy.

6.3.14 TLS Management

Information regarding TLS prophylaxis is provided in Section 6.2.1.2.

Subjects must be monitored for TLS on C1D1 through C1D5 with assessment of vital signs, AEs, and serum chemistry and hematology laboratory studies as described in Section 7. Subjects who develop TLS may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, acute renal failure, and cardiac dysrhythmias; thus, close monitoring of electrolytes, serum creatinine, and vital signs is particularly important after initial therapy. ECG monitoring should also be instituted in subjects with biochemical abnormalities suggestive of TLS.

Subjects with TLS should receive IV hydration, rapid reversal of hyperkalemia, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. LAM-003 administration may continue except in those who develop Grade 4 TLS or Grade 3 TLS associated with Grade ≥2 renal dysfunction or other Grade ≥2 end-organ injury. Upon recovery to baseline functioning and as medically appropriate, subjects who develop TLS should continue with protocol therapy to maintain tumor control.

6.4 Study Restrictions

6.4.1 Breast Feeding

There is no information regarding the presence of LAM-003, LAM-003A, or other metabolites in human milk; the potential effects of the drug or its metabolites on the breastfed infant, or the potential effects of the drug or its metabolites on milk production. For these reasons women who are nursing are not eligible to participate in this study. Lactating women who do participate in this clinical trial must discontinue nursing during study therapy.

6.4.2 Contraception/Reproduction

In general toxicology studies, LAM-003A administration was not associated with adverse histopathological effects on organs of reproduction at exposures that are likely to be achieved clinically. However, no studies evaluating drug effects on reproductive function in animals or humans are available. Thus, subjects should be advised that the risks of LAM-003 for future reproduction are unknown.

No nonclinical data or clinical data are available regarding LAM-003 or LAM-003A effects during embryo-fetal development. Accordingly, female subjects cannot be pregnant at the time of study entry and must be removed from study therapy if they do become pregnant.

Sexually active females of childbearing potential must agree to use a protocol-recommended method of contraception during heterosexual intercourse from the start of the screening period until ≥30 days after the final dose of study therapy. In the context of this protocol, a female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional laboratory postmenopausal range and a negative serum or urine beta human chorionic gonadotropin [βHCG]); or is menopausal (age ≥50 years with amenorrhea for ≥6 months).

Sexually active male subjects who can father a child and are having intercourse with females of childbearing potential who are not using adequate contraception must agree to use a protocol-recommended method of contraception from the start of study therapy until ≥30 days after the final dose of the study therapy and to refrain from sperm donation from the start of study therapy until ≥90 days after administration of the final dose of study therapy. In the context of this protocol, a male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.

Protocol-recommended contraceptive methods are described in Table 2.

Table 2: Protocol-Recommended Contraceptive Methods

Individual Methods	Combination Methods	
	Hormonal Methods (One method to be used with a barrier method)	**Barrier Methods (Both methods to be used OR one method to be used with one hormonal method)**
IUD (eg, Copper T380A, LNg20)	Estrogen and progesterone	Diaphragm with spermicide
Tubal sterilization	Oral contraceptives	Male condom (with spermicide)
Hysterectomy	Transdermal patch	
Vasectomy	Vaginal ring	
	Progesterone injection or implant	

Abbreviation: IUD=intrauterine device

6.4.3 Diet

Pending the acquisition of information regarding the effects of food on LAM-003 pharmacokinetics, subjects should be encouraged to fast (with the exception of clear liquids) for ≥2 hours before and ≥1 hour after each LAM-003 dose.

Subjects should be advised to avoid ingestion of grapefruit, grapefruit juice, Seville oranges, or starfruit (all of which contain CYP3A4 inhibitors) and should not use St. John's wort (which is a potent CYP3A4 inducer).

No other specific dietary restrictions are required.

6.5 Duration of Study Drug Administration and Study Participation

Subjects may receive LAM-003 therapy indefinitely. However, the occurrence of any of the following events requires treatment discontinuation:

- Subject request to withdraw from study treatment
- Documented objective evidence of treatment failure or of AML relapse or progression (see Section 10.4.5 and Section 10.4.6 for definitions) while receiving study treatment at the highest individually tolerated dose level
- For a subject in PR, continued red blood cell transfusion dependence at Week 20
- Intolerable toxicity despite appropriate supportive care and/or dose modification
- Failure to recover to Grade ≤1 or baseline within 2 weeks from the last dose of LAM-003 following interruption for a TEAE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication
- The development of intercurrent illness or other substantial change in the subject's condition or circumstances that would place the subject at unacceptable risk as determined by the study investigator in consultation with the medical monitor
- Initiation of treatment for the subject's cancer with an off-study therapeutic regimen
- Pregnancy or breastfeeding
- Substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results
- Discontinuation of the study by the study center, the study sponsor, relevant regulatory agencies, or the IRB/IEC

Unless they withdraw consent for further follow-up, subjects who discontinue study therapy will continue on study for acquisition of safety information through ≥30 days after the last dose of study treatment, and for further collection of information regarding additional therapies for their cancer and OS.

6.6 Rationale for Study Drug Administration and Supportive Care

The initial cohort of subjects in this study will be prescribed 200 mg QD; this dose level is 2.4-fold below the RDR of 480 mg total daily dose established as tolerable in the prior Phase 1 study of LAM-003A in patients with solid tumors. While offering all participants the potential for antitumor efficacy, this starting dose level provides a safety margin to account for the status of LAM-003 as a previously untested prodrug of LAM-003A and the lack of experience with use of the drug in a hematological cancer (for which TLS could represent a potential safety concern).

Both one-per-day (QD) and twice-per-day (BID) dosing were explored in the Phase 1 study of LAM-003A in patients with solid tumors. It appeared that the total daily dose of LAM-003A was most important in defining the safety profile; the study did not suggest a schedule-dependent safety concern with either the QD or BID dosing regimen. Further, the average half-life ($t_{1/2}$) after repeated dosing of LAM-003A was 11.2 hours, supporting use of either QD or BID dosing. Based on these observations, the current study will initially evaluate LAM-003 using a QD

dosing regimen because such dosing could potentially minimize the likelihood of TLS (by avoiding administration of a C1D1 evening dose in the face of potential TLS-mediated renal dysfunction). In addition, food-effect data are not yet available; thus, QD dosing in the morning is appropriate to increase the likelihood that the drug will consistently be administered in a fasting state. Further, QD dosing offers convenience advantages for patients. BID dosing may be explored in this protocol once there is more safety, pharmacokinetics, and pharmacodynamic experience with the drug using the initial QD regimen.

The dose modification provisions are designed to balance a primary concern for subject safety with the potential for observing pharmacological and antitumor activity in circumstances in which a subject experiences an AE that justifies a dose reduction but can continue on therapy at a lower LAM-003 dose level. Focusing dose modifications to the prespecified dose levels permit the acquisition of greater chronic safety experience at the dose levels prescribed by the protocol. Allowing sequential dose reductions is consistent with typical oncological practice and permits maximum benefit for participants. Further, this approach generates additional chronic safety data and information regarding rechallenge or tachyphylaxis to drug effects. This method also provides dose modification data that can inform the dose modification plan in future LAM-003 development.

Supportive care recommendations consider widely used approaches in the management of toxicities relating LAM-003 and other cancer products in patients with hematological cancers. Suggestions for TLS prophylaxis are based on established guidelines relevant to AML [Cairo 2010, MDACC 2013, Ejaz 2015]. Management of ophthalmologic adverse events is consistent with approaches taken in the development of other HSP90 inhibitors [Sessa 2013, Bendell 2015, Shapiro 2015, Bendell 2016, Kong 2016]). A systematic approach to use of concomitant medications minimizes confounding effects on evaluation of study therapy pharmacokinetics and pharmacodynamics while establishing supportive care regimens to maintain subject safety and inform toxicity management recommendations for further development.

7 STUDY ACTIVITIES AND ASSESSMENTS

The specific study procedures and time of activities to be conducted for each subject enrolled in the study are presented in tabular form in Table 3. Physical examinations, other clinical evaluations, and additional laboratory studies or more frequent assessments may be performed consistent with appropriate medical care for the subject, but these data will not necessarily be collected unless specified in Table 3.

Missed or delayed procedures or evaluations should be performed as close to the originally scheduled date/time as possible. Based on the investigator's judgment, an exception can be made when rescheduling becomes medically unnecessary because it is too close in time to the next scheduled procedure or evaluation. In that case, the missed evaluation may be omitted after consultation with the medical monitor.

Table 3: Schedule of Activities

Study Period/Cycle	Screening	Therapy											Posttherapy Follow-up	
		Cycle 1							Cycle 2		Cycle ≥3	End of Therapy Visit		
Day	-28 to -1 [a]	1 [b]	2	3	4	5	8	15	1	15	1		≤30 days	Long-term
Visit Window, days							±2	±3	±3	±3	±3	+14		
General Eligibility/Safety Assessments														
Written informed consent [c]	X													
Medical history [d]	X													
Height [e]	X													
Weight [f]	X	X	X	X	X	X	X		X		X	X		
Vital signs/oxygen saturation [g]	X	X	X	X	X	X	X		X		X	X		
Performance status [h]	X	X					X		X		X	X		
AE assessment [i]	X	X	X	X	X	X	X	X [i]	X	X [i]	X	X	X	
Concomitant medications [j]	X	X	X	X	X	X	X	X [i]	X	X [i]	X	X	X	
12-lead ECG [k]	X	X	X				X		X			X		
Ophthalmological examination [l]	X								X [l]		X [l]	X		
Study Drug Administration/Dispensing/Return														
TLS prophylaxis as needed [m]	X	X												
LAM-003 administration in clinic [n]		X	X	X	X	X	X							
Dispensing of LAM-003 [o]						X			X		X			
LAM-003 return/compliance and diary check [p]									X		X	X		
Laboratory Assessments														
Urinalysis [q]	X	X	X						X			X		
Serum virology [r]	X													
Serum pregnancy test [s]	X	X							X		X	X		
Serum chemistry [t]	X	X	X	X	X	X	X	X [t]	X	X [t]	X	X		
Hematology [u]	X	X	X	X	X	X	X	X [u]	X	X [u]	X	X		
Coagulation [v]	X	X	X						X			X		
Plasma for LAM-003 pharmacokinetics [w]		X	X				X							
Blood for AML FLT3/HSP protein expression [x]		X	X				X		X					
Blood for AML HSP gene expression [y]		X	X				X		X					
Plasma for FL concentrations [z]		X	X				X		X					
Blood for AML PD-L1 expression [aa]		X	X				X		X					
Blood for immune cell profiling [bb]		X					X		X					
Disease-Related Assessments														
AML genetic profiling data from records [cc]	X													
Blood and/or bone marrow for FLT3 mutation [dd]	X													
Blood/saliva for AML/control mutation profiling [ee]		X												
Blood and bone marrow aspiration/biopsy [ff]	X										X [ff]	X [ff]		
Radiology examination [gg]	X										X [gg]	X [gg]		
Posttherapy Follow-up														
Posttherapy safety assessment [hh]													X	
Long-term follow-up [ii]														X

Footnotes	
N*ote:*	***For scheduled visits after C1D1, permitted visit windows are indicated in the table. For procedures to be performed at a specified time postdose, the acceptable margin for actual time is as follows for hours (±minutes): 0.5 (±5), 1 (±15), 2 (±15), 4 (±15), 6 (±15), 8 (±15), 24 (±60). If multiple procedures are to be done at the same timepoint, the preferred order is vital signs, blood sampling, and then ECG, with blood sampling occurring as close as possible to the specified time.***
a.	To optimize scheduling convenience for the subject and for the study center staff, Screening procedures may be performed over as many days as necessary provided that screening activities (excepting prestudy tumor evaluation) are completed within 28 days before C1D1 of the study.
b.	If obtained within 3 days prior to the start of therapy, urinalysis and serum pregnancy, serum chemistry, hematology, and coagulation studies collected during Screening need not be repeated on C1D1.
c.	Written informed consent will be obtained before performance of any study procedures that are not part of routine medical care.
d.	Medical history to include recording of cancer history, previous therapy for cancer, past and ongoing medical conditions, review of systems, and relevant social history.
e.	Height (in centimeters) will be obtained at Screening only.
f.	Weight (in kilograms) will be obtained once on each designated day.
g.	Vital signs (blood pressure, pulse, temperature, and oxygen saturation via pulse oximetry) will be obtained with the subject resting in a supine position while breathing room air. Vital signs will be 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), C2D1, C≥3D1, and at End of Therapy.
h.	Performance status will be assessed using ECOG scale (see Appendix 14.1) once on each designated day.
i.	AEs will be described using concise medical terminology, including whether serious, the date of onset, the date of resolution, severity based on the CTCAE (Version 4.03) [NCI 2010], a description of potential relatedness to the study drug or to a study procedure, the action taken due, and the outcome. On C1D15 and C2D15, AE information may be obtained via telephone contact with the subject.
j.	Concomitant medication assessments should include information regarding all prescription, nonprescription, illicit, and alternative medications (health foods). Use of any supportive care (eg, antiproliferative drugs, antidiarrheals, antiemetics, hematopoietic growth factors, transfusions) should be noted. On C1D15 and C2D15, concomitant medication information may be obtained via telephone contact with the subject.
k.	12-lead ECGs will be obtained with the subject resting in a supine position. ECGs will be collected at Screening, C1D1 (predose [in triplicate], 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.
l.	Ophthalmologic evaluations (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography) should be performed by an ophthalmologist, optometrist, or other qualified specialist during Screening, within 14 days before C2D1 (4-week interval), within 14 days before C4D1 (8-week interval), and then within 14 days before C7D1, C10D1, C13D1, C16D1, etc (12-week intervals), and at End-of-Therapy. An End-of-Therapy ophthalmologic evaluation may be omitted with the approval of the medical monitor.
m.	If TLS is observed during study conduct, subjects who are at intermediate or high risk of TLS should receive medical prophylaxis according to the protocol-recommended or an institutional regimen customarily used at the study center (see Section 6.2.1.2).
n.	The dose of LAM-003 will be administered to the subject in the study center (with recording of the date and actual clock time of the LAM-003 administration). On C1D2, C1D3, C1D4, and C1D5, LAM-003 should only be administered after the serum chemistry results from that day have been evaluated to exclude Grade 4 TLS or Grade 3 TLS associated with Grade ≥2 renal dysfunction or other Grade ≥2 end-organ injury.
o.	Study centers will ensure that subjects have a sufficient supply of LAM-003 and are provided with instructions for self-administration at home.
p.	Empty, partially used, or full bottles of LAM-003 will be retrieved from the subject and drug compliance will be assessed. In addition, the subject's dosing diary should be reviewed, any incomplete or inconsistent entries should be addressed, and the dosing diary should be photocopied.
q.	Urinalysis to include specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick and white blood cells, red blood cells, epithelial cells, bacteria, cast and crystals as assessed by microscopy. Urinalysis should be performed once on each designated day.
r.	Virology evaluation to include serum HIV antibody, HbsAg antibody, HBc antibody, HCV antibody. Subjects with a positive antibody evaluation for HBc or HCV should undergo evaluation for HBV DNA and for HCV RNA to determine if the antibody test may be falsely positive.
s.	Serum pregnancy testing will be performed in women of childbearing potential only. Pregnancy testing should be performed once on each designated day.
t.	Serum chemistry studies to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT,

	AST, ALP, CK, LDH, total bilirubin, uric acid. Serum chemistry studies should be performed once on each designated day. On C1D2, C1D3, C1D4, C1D5, serum chemistry results from that day should be evaluated for evidence of Grade 4 TLS or Grade 3 TLS associated with Grade ≥2 renal dysfunction or other Grade ≥2 end-organ injury before the subject is administered LAM-003 in the clinic. On C1D15 and C2D15, serum chemistry studies may be obtained at a local laboratory.
u.	Hematology to include hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils; platelet count. Hematology testing should be performed once on each designated day. On C1D15 and C2D15, hematology studies may be obtained at a local laboratory.
v.	Coagulation studies to include PT and aPTT. Coagulation studies should be performed once on each designated day.
w.	Plasma for LAM-003 pharmacokinetics will be collected on C1D1 (predose, and at 0.5, 1, 2, 4, 6, and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), and on C1D8 (predose, and at 0.5, 1, 2, 4, 6, and 8 hours postdose).
x.	Blood for FLT3 /HSP protein expression in AML blasts will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.
y.	Blood for HSP gene expression will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.
z.	Plasma for FLT3 ligand concentrations will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.
aa.	Blood for AML PD-L1 expression will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.
bb.	Blood for immune cell profiling will be collected on C1D1 (predose), C1D8 (predose), and C2D1.
cc.	Any available information in medical records regarding AML genetic profiling (eg, for FLT3 mutation status) to be collected for sponsor review.
dd.	Blood and/or bone marrow aspirate for FLT3 mutation confirmation in AML blasts using a sponsor-specified assay will be obtained during Screening.
ee.	Blood for AML cell mutation profiling with collection of saliva as a germline DNA control will be obtained on C1D1 (predose).
ff.	Blood for peripheral blood AML blast count evaluation and bone marrow aspiration/biopsy will be performed during Screening (unless the requirement for screening bone marrow aspirate/biopsy is waived by the medical monitor because sufficient bone marrow material is available for response determination). Post-baseline, a peripheral blood AML blast count evaluation and a bone marrow aspirate/biopsy is required within 14 days before C3D1, C5D1, C7D1 (8-week intervals), and then within 14 days before C10D1, C13D1, C16D1, etc (12-week intervals). An End-of-Therapy peripheral blood AML blast count evaluation and a bone marrow aspirate/biopsy should be performed unless the subject already has hematological or radiographic confirmation of TF or DRP ≤8 weeks before permanent study drug discontinuation or the medical monitor approves omission of such End-of-Therapy testing. At all AML evaluations, the extent of involvement with AML in peripheral blood and bone marrow, the presence of Auer rods, and bone marrow cellularity will be assessed. Bone aspirate aliquots obtained at Screening and within 14 days before C3D1 may also be evaluated for FLT3/HSP protein and gene expression, PD-L1, and AML mutations.
gg.	Radiology examination is required in subjects with extramedullary disease that is radiographically assessable. FDG-PET/CT is the preferred method of evaluation but other methods (diagnostic CT, MRI) may be used if appropriate for the type of lesion. The baseline evaluation should occur within 28 days before C1D1. Post-baseline evaluations should be performed within 7 days before C3D1, C5D1, C7D1 (8-week intervals), and then within 7 days before C10D1, C13D1, C16D1, etc (12-week intervals). An End-of-Therapy radiology assessment should be performed unless a subject with extramedullary disease already has hematological or radiographic confirmation of TF or DRP ≤8 weeks before permanent study drug discontinuation or the medical monitor approves omission of such End-of-Therapy testing.
hh.	Posttherapy safety assessment will be performed after permanent cessation of study therapy to follow subjects for any drug-related AE and/or ongoing SAEs. Subjects will be followed until the later of either 30 days after the last dose of study treatment or until resolution/stabilization of any ongoing drug-related AEs and/or SAEs. Follow-up may be obtained in person or by telephone contact.

ii. Long-term follow-up information will be obtained in all surviving subjects who permanently discontinue study therapy. Data on post-study therapies for the AML and on survival will be collected. Such information may be collected at ~3- to 6-month intervals through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: AE=adverse event, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AML=acute myeloid leukemia, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CK=creatine kinase, CT=computed tomography, CTCAE=Common Terminology Criteria for Adverse Events, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, FDG=fluorodeoxyglucose, FL=FLT3 ligand concentration, FLT3= FMS-like tyrosine kinase-3, HBc antibody=hepatitis B core antibody, HbsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HSP=heat shock protein, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, PD-L1=programmed death-ligand 1, PET=positron emission tomography, PT=partial thromboplastin time, RNA=ribonucleic acid, SAE=serious adverse event, TLS=tumor lysis syndrome

8 SAFETY ASSESSMENTS

8.1 Definitions

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product; the event does not necessarily have a causal relationship with study drug administration or usage. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In this study, any of the following events will be considered an AE:

- Any complication that occurs as a result of a protocol-mandated procedure (eg, venipuncture, ECG).
- Any preexisting condition that increases in severity or changes in nature during or as a consequence of study drug administration. Worsening manifestations of the underlying cancer (eg, increase in pain, tumor flare reaction, TLS) may be considered AEs in this study.
- Any injury or accident. If a medical condition is known to have caused the injury or accident (eg, a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs.
- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Any laboratory (eg, clinical chemistry, hematology, urinalysis) or investigational abnormality (eg, ECG, X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test), or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (eg, anemia) not the laboratory result (eg, decreased hemoglobin) should be recorded.
- A complication related to pregnancy or termination of a pregnancy (see Section 8.7.2 for additional information).

None of the following events is considered an AE:

- Asymptomatic hyperleucocytosis
- Cancer progression without worsening disease manifestations. In cases of SAEs, cancer progression may be reported if there is no alternative term that can be satisfactorily substituted. In such cases, the AE description should match the SAE description.
- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of laboratory monitoring.

- A diagnostic, medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, transfusion). However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded in the source documents.
- A preexisting disease or condition or laboratory abnormality present or detected before the initial screening visit and that does not worsen.
- An intervention not associated with an untoward medical occurrence (eg, hospitalization for elective surgery or for social and/or convenience reasons).
- An overdose without clinical sequelae.

8.1.2 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that results in any of the following outcomes:

- Death (ie, all deaths occurring between signing of the consent form to within 30 days after last study drug administration), including deaths due to cancer progression if no other event more satisfactorily explains the reason for death. Deaths that occur as a result of an AE that started during the study period should be reported. Death is not an SAE term; the reported AE should be the event that caused the death. Death is the outcome of this SAE.
- Life-threatening situation (ie, with an immediate risk of death from the event as it occurred but not including an event that, had it occurred in a more serious form, might have caused death).
- In-patient hospitalization or prolongation of existing hospitalization. Of note, an untoward medical occurrence that occurs during hospitalization is an AE but a complication that prolongs hospitalization is an SAE. In-subject hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions or prolongations of hospitalization for administration of the study drug or procedures required by the study protocol, diagnostic observations or procedures, administration of concomitant or subsequent therapy for the cancer, logistical issues (eg, lengthy travel), or the convenience of the subject or clinical personnel are not considered serious.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect in the offspring of a subject who received the investigational medicinal product.
- Other medically significant event. Such events may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events might include:
    - Allergic bronchospasm requiring intensive treatment in an emergency room or at home
    - New cancers or blood dyscrasias

- Convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

8.1.3 Unexpected Adverse Event

An unexpected AE is defined as an event that has a nature, severity, or specificity that is not consistent with the applicable investigator brochure, or that is symptomatically and pathophysiologically related to a known toxicity but differs because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

8.1.4 Treatment-Emergent Adverse Event

A TEAE is defined as an AE that occurs or worsens in the period from the first dose of study drug administration to 30 days after the final dose of study drug administration.

8.1.5 Adverse Events of Special Interest

The major AEs of special interest in this protocol will be any occurrences of TLS or ophthalmological symptoms or signs. In addition to descriptions in listings and tables, narratives will be prepared to describe the clinical and laboratory manifestations of these outcomes.

8.2 Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject should be questioned about AEs at each scheduled study center visit or during any telephone contact with the subject. The type of question asked should typically be open-ended, eg, "Have you had any new health problems?" or a similar type of query.

8.3 Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the electronic case report forms (eCRFs). The following considerations apply in collecting AE information:

- Recognized medical terms (not colloquialisms, abbreviations, or jargon) should be used when recording AEs. Ideally the description should be consistent with MedDRA nomenclature.
- The medical diagnosis (ie, disease or syndrome) should be recorded instead of signs and symptoms (eg, pneumonia instead of shortness of breath, coughing, and fever).
- Any sign or symptom considered as unrelated to an encountered disease or syndrome should be recorded as an individual AE (eg, if nausea and severe headache are observed at the same time, each event should be recorded as a separate AE).

- If an AE resolves and reoccurs at a later date, a new AE must be documented and reported, as appropriate.

The following information should be recorded:

- Description as to whether the AE is serious, if applicable (see Section 8.1.2)
- The start date (date of AE onset)
- The stop date (date of AE resolution)
- The severity of the AE (see Section 8.4)
- A description of the relatedness of the AE to the study drug or to a study procedure (see Section 8.5)
- The action taken due to the AE
- The outcome of the AE

8.4 Grading of the Severity of an Adverse Event

The severity of AEs will be graded and reported using the CTCAE, Version 4.03 [NCI 2010].

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 4.

Table 4: Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events (as listed in Section 8.1.2).

8.5 Describing Adverse Event Relationship to Study Drug and Study Procedures

The investigator will evaluate the causal relationship of each AE to a study drug and/or to a study procedure (eg, venipuncture or ECG evaluation) and record that relationship on the appropriate CRFs. Causality will be assessed considering whether the AE is reasonably related to

the study drug or procedure or whether the AE is not reasonably related to the study drug or procedure considering the definitions in Table 5.

Table 5: Relationship of Study Drug to Adverse Event

Relationship	Description
Definite	A clinical event in which a relationship to the use of the study drug seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Possible	A clinical event with a reasonable temporal association with administration of the study drug, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Unlikely	A clinical event with a temporal relationship to study drug administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.
Unrelated	A clinical event in which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.

8.6 Adverse Event Reporting Period

The start of the AE reporting for a study subject will coincide with signing of the informed consent for this study. Between the time of informed consent and the first administration of study drug, only AEs (nonserious and serious) assessed as related to study procedures should be reported. After the first administration of study drug, all AEs (serious and nonserious, related and unrelated) should be reported. Unless a subject withdraws consent for follow-up, each subject must be followed until the end of the AE reporting period at 30 days after the final LAM-003 administration or when any ongoing drug-related AEs and/or SAEs have resolved or become stable. The investigator should use appropriate judgment in ordering additional tests as necessary to monitor the resolution of events. The medical monitor or the sponsor may request that certain AEs be followed longer.

Investigators are not obligated to actively seek information regarding the occurrence of new SAEs beginning after the 30-day post-LAM-003 period. However, if the investigator learns of such an SAE and that event is deemed relevant to the use of LAM-003, he/she should promptly document and report the event. A longer reporting period applies in the case of pregnancy (see Section 8.7.2).

8.7 Study Center Reporting Requirements

8.7.1 Adverse Event Reporting Requirements

Classification of an event as serious or nonserious (see Section 8.1) determines the reporting procedures to be followed by the study center. Study center reporting requirements for AEs are summarized in Table 6.

Table 6: Study Center Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours of becoming aware of the event	E-mail report on designated SAE report form to the sponsor or designee [a] and to the study center IRB, as per local IRB/IEC requirements
	Within 10 working days	E-mail copies of relevant source documents (eg, progress notes, laboratory and diagnostic test results, discharge summaries) [b] to the sponsor or designee [a].
	Per eCRF submission procedure	Record and submit information on appropriate eCRFs.
Nonserious	Per eCRF submission procedure	Record and submit information on appropriate eCRFs.

a. See contact information in Table 7.
b. Subject name, address, and other personal identifiers should be obscured but without losing the traceability of a document to the study subject identifiers.

Abbreviations: eCRF=case report form; IRB/IEC= institutional review board/independent ethics committee; SAE=serious adverse event

For SAEs, in addition to completing the AE portion of the eCRF, an SAE report form must also be completed and emailed within 24 hours of first awareness of the event to the sponsor (or designee) (see Table 7).

Investigators must also submit written safety reports as required by the IRB/IEC within timelines set by local and regional regulations. The study site should retain documentation of the submission of expedited safety reports to the IRB/IEC, and their receipt. Study site personnel should not wait to receive complete information or the investigator's signature before notifying the sponsor (or designee) and the IRB/IEC of an SAE.

The following minimum information is required:

- Subject identification (ie, subject number, sex, age)
- Description of the SAE (diagnosis preferred, symptoms, etc)
- Study drug and causal relationship of the SAE to the study drugs or study procedures
- Investigator name

Collection of complete information concerning SAEs is extremely important. The information in the AE portion of the eCRF and the SAE report form must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

All available and relevant supporting documentation (eg, progress notes, pertinent laboratory and diagnostic test results, discharge summaries) should also be provided. The subject's name,

address, and other personal identity information should be obscured on any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries). The subject's unique study number should be included on each page of any document provided.

The sponsor (or designee) will review SAE reports for missing information and send queries to the site for resolution as indicated. The study site is responsible for obtaining pertinent follow-up information missing from initial reports and forwarding the information within 24 hours of receipt to the sponsor (or designee). Follow-up information to the SAE should be clearly documented as "follow-up" in the SAE report form.

The original SAE form and any follow-up forms must be kept on file at the study site. An SAE is followed until it is considered resolved, it returns to baseline, is chronically ongoing, or explained otherwise by the principal investigator.

8.7.2 Pregnancy

Each female subject should be instructed to inform the investigator immediately if she becomes pregnant at any time between the start of study screening until 30 days after the last administration of study drug.

The investigator should counsel the subject regarding the possible effects of study drug exposure on the fetus and the need to inform the study center, the medical monitor, and the sponsor (or designee) of the outcome of the pregnancy.

Neither the pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an AE; such occurrences should be reported on the appropriate pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as an SAE (ie, spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs (ie, report the event to the sponsor [or designee] and follow up by submission of the appropriate AE eCRFs (see Section 8.7.1).

Additional information about pregnancy outcomes that are classified as SAEs includes:

- Any spontaneous abortion, including miscarriage and missed abortion, will be reported as an SAE.
- An induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons will be recorded as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in-utero exposure to the study drug should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, there is no required minimum follow-up of a presumably normal infant before the pregnancy outcome report eCRF can be completed).
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly, in which case pathologic examination should be requested.

Information regarding any pregnancy in a study subject or the female partner of a male subject must be documented on a pregnancy report form and forwarded to the sponsor (or designee) (see Table 7) within 24 hours of becoming aware of the pregnancy. Monitoring of the pregnancy in both female study subjects and female partners of male study subjects should continue until the conclusion of the pregnancy. For female partners of male study subjects, such monitoring applies if the pregnancy occurs in the period from the subject's start of study drug until 30 days after the subject's last dose of study drug. The outcome of the pregnancy should be reported on the pregnancy outcome report form within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported to the sponsor (or designee) (see Table 7).

8.7.3 Contact Information for Reporting an SAE or Pregnancy

Contact information for reporting an SAE or pregnancy is provided in Table 7.

Table 7: Contact Information for Reporting SAEs or Pregnancies

Pharmacovigilance CRO	Contact Information
Pharmalex US, LLC, Guilford, CT, USA	E-mail: Vigicare@pharmalex.com
	Facsimile: +1 (617) 315-4825

CRO=contract research organization, SAE=serious adverse event

8.8 Sponsor Reporting Requirements

Each SAE or special situation report received from the investigator will be evaluated by the sponsor (or designee). The sponsor (or designee) will assess the seriousness of the event (see Section 8.1.2), the expectedness of the event (see Section 8.1.3), and the relationship to participation in the study (see Section 8.5). The sponsor (or designee) will also indicate whether there is concurrence with the details of the report provided by the investigator.

The sponsor (or designee) will provide information for reporting of suspected, unexpected, serious adverse reactions (SUSARs) to regulatory authorities worldwide consistent with relevant

legislation or regulations, including the applicable US FDA CFR, the European Commission Clinical Trials Directive (2001/20/EC, and revisions), and other country-specific legislation or regulations. SUSARS will be reported to regulatory authorities within 7 calendar days for life-threatening and fatal events, or 15 calendar days for all others. These timeframes begin with the first notification of the event from the reporting investigator to the sponsor (or designee), which represents the start of the regulatory clock (Day 0).

The sponsor (or designee) will also provide all investigators with a safety letter describing the SUSAR. The information will be provided by e-mail, fax, or overnight mail within 15 calendar days from Day 0. Investigators will be requested to provide written notification of the event to the relevant IRB/IEC as soon as is practical and consistent with local regulatory requirements and local institutional policy.

9 LABORATORY AND OTHER ASSESSMENTS

9.1 Methods and Analytes

Samples to be obtained and parameters to be analyzed are indicated in Table 8.

General safety laboratory assays (serum virology, serum pregnancy test, serum chemistry, hematology, coagulation, urinalysis) will be performed using standard clinical pathology methods at Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories associated with the study centers.

For pharmacokinetic analyses, evaluation of LAM-003 serum concentrations will be performed using a validated immunoassay at a contract laboratory designated by the sponsor.

Cellular pharmacodynamic assessments from peripheral blood and bone marrow will be assessed at the sponsor or at contract laboratories designated by the sponsor. Similarly, plasma analyses for FL3 ligand will be analyzed by immunoassays at the sponsor or sponsor-specified contract laboratories.

FLT3 mutation analysis in AML blasts using a FLT3 mutation assay will be performed at the sponsor or at a sponsor-designated contract laboratory.

Any available information in the subject medical records regarding AML genetic profiling (eg, for FLT3 mutation status) will be provided in redacted format for sponsor review.

Efficacy evaluations of bone marrow aspirates and biopsies will be performed by a sponsor-specified CRO specializing in central pathology review of AML clinical trials.

Clinical assessments (body weight and height, vital signs, oxygen saturation) will be obtained using standard clinical equipment available at each study center.

Ophthalmological examinations should be performed by a consulting ophthalmologist, optometrist, or other qualified specialist with the necessary facilities and equipment to perform appropriate testing (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography); interpretations of ophthalmological findings will be provided by a consulting specialist.

ECGs will be performed at the clinical sites using ECG machines provided by a LAM-specified CRO; study-specific interpretations of the ECG findings will be provided by a cardiologist at the CRO.

Radiography testing performed in subjects with extramedullary disease will be performed and interpreted at study centers.

Table 8: Laboratory and Other Parameters to Be Assessed

Test/Procedure	Parameters
Laboratory – Safety	
Serum virology	• Serum HIV antibody • Serum HbsAg antibody, HBc antibody (if positive, then serum HBV DNA by PCR) • Serum HCV antibody (if positive, then serum HCV RNA by PCR)
Serum pregnancy test	• Serum β-HCG
Serum chemistry	• Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, ALP, CK, LDH, total bilirubin, uric acid.
Hematology	• Hematocrit, hemoglobin, erythrocyte count • Absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils • Platelet count
Coagulation	• PT • aPTT
Urinalysis	• Dipstick: specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase • Microscopy: White blood cells, red blood cells, epithelial cells, bacteria, casts, crystals
Laboratory – Pharmacokinetic	
Plasma pharmacokinetics	• Plasma LAM-003 and LAM-003A concentrations (as assessed by validated bioassays) • Retention of plasma for potential metabolite analyses
Laboratory – Pharmacodynamic	
Peripheral blood and bone marrow aspirate cellular pharmacodynamics	• 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) • HSP gene expression in AML blasts (as measured using quantitative PCR) • PD-L1 expression in AML blasts (as measured using flow cytometry)
Plasma pharmacodynamics	• Plasma concentrations FL (as measured using an immunoassay) • Retention of plasma for potential additional cytokine/chemokine analyses, LAM-003 concentration analysis, or alternative safety parameter analysis
Peripheral blood immunoprofiling	• Numbers of circulating B-cell, T-cell, NK, and monocyte subsets, potentially including (but not limited to): B cells (CD19, B regulatory cells (CD19+, CD38+, CD1d+, IgM+, CD147+), total T cells (CD3+), cytotoxic T cells (CD3+, CD8+), activated cytotoxic T cells (CD3+, CD8+, Granzyme B+, Perforin+, IFNγ+, PD1+), NK cells (CD3-, CD56+, CD16+), mature/activated NK cells (CD3-, CD56 dim, CD16+, CD57+, Perforin+, GranzymeB+, IFNγ+), and NK-T cells (CD3+, CD56+) (as measured using flow cytometry)

Table 8: Laboratory and Other Parameters to Be Assessed

Test/Procedure	Parameters
Laboratory – Disease-related	
Peripheral blood or bone marrow cellular AML FLT3 mutation analysis	• Peripheral blood or bone marrow AML blast FLT3 mutation type and FLT3 mutation-to-WT allele ratio (as evaluated using a sponsor-specified FLT3 mutation assay)
Baseline biomarker assessment	• Mutational profiling in DNA from peripheral blood AML blasts with saliva as germ-line DNA control (with sample analysis using NGS)
Peripheral blood smears and bone marrow aspirate and biopsy for efficacy assessments	• Peripheral blood smears and bone marrow aspirate and biopsy for analysis of AML disease status (blast percentage, presence of Auer rods, bone marrow cellularity, MRD) (as assessed by Wright stain for peripheral blood and bone marrow aspirate, hematoxylin and eosin for bone marrow biopsy, flow cytometry, and immunohistochemistry [as needed for ambiguous blast analysis])
Other	
Body weight/height	• Weight in kilograms, height in centimeters
Body temperature	• Temperature in degrees Celsius
Blood pressure	• Diastolic and systolic blood pressure in mm Hg
Oxygen saturation	• % saturation
Ophthalmology examination	• Examination by an ophthalmologist, optometrist, or other qualified specialist (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography))
12-lead ECG	• Heart rate, cardiac intervals, wave form abnormalities, ectopy
Radiology examination	• FDG-PET/CT (preferred), MRI, or diagnostic CT imaging for subjects with extramedullary disease that is radiographically assessible.

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AML=acute myeloid leukemia, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CD=cluster of differentiation, CK=creatine kinase, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, FDG=fluorodeoxyglucose, FL=FLT3 ligand, FLT3= FMS-like tyrosine kinase-3, HBc antibody=anti-hepatitis B core antibody, HbsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HSP=heat shock protein, IFNγ=interferon-γ, LDH=lactate dehydrogenase, MRD=minimal residual disease, MRI=magnetic resonance imaging, NGS=next-generation sequencing, NK=natural killer (cells), PET=positron emission tomography, PCR=polymerase chain reaction, PD-L1=programmed death (receptor) ligand-1, PT=prothrombin time, RNA=ribonucleic acid, WT=wild-type, β-HCG=β-human chorionic gonadotropin.

9.2 Sample Shipping, Storage, and Retention

Routine clinical safety samples (for serum virology, serum pregnancy test, serum chemistry, hematology, and coagulation) will be analyzed at the clinical laboratory at the study center and will not be shipped. These samples will not be stored and will be discarded promptly after analysis.

Other samples (plasma for pharmacokinetics; blood, bone marrow, and plasma for pharmacodynamics and immune profiling; bone marrow for disease characterization) will be prepared following the instructions outlined in a detailed clinical study laboratory manual.

These samples will be shipped to the sponsor or the contract analytical laboratories using a shipping service designated by the sponsor and as specified in the study laboratory manual. For

the duration of the sample analysis campaign, samples will be stored at these contract laboratory facilities or sent for long-term storage at a storage facility designated by the sponsor. Samples will be retained as described for study records (see Section 12.7).

As described for other study records (see Section 12.7), copies of data relating to body weight and height, vital signs, oxygen saturation, and radiography will be retained on file at the study centers. The sponsor may request copies of primary radiography images (redacted of subject personal identifying information) for storage at the company. Copies of data relating to ECG parameters and bone marrow biopsy/aspirate data will be retained on file at the CROs responsible for analysis of those data.

10 EFFICACY ASSESSMENTS

10.1 Overview

The determination of remission and progression for AML in this study will be based on standardized criteria [Cheson 2003, Döhner 2017] as modified for use in the context of protocol therapy for relapsed or refractory AML. During the study, investigators will periodically determine AML disease status. Treatment decisions by the investigator in this study will be based, in part, on these assessments. Bone marrow assessments will be subject to independent review and together with peripheral blood and any radiographic information these data will be considered primary for analyses of tumor control.

10.2 Methods of Assessment

Evaluation of peripheral blood cell counts and bone marrow aspirates will be used in this study as the primary basis of AML assessment, but with consideration of extramedullary disease for subjects who have such involvement.

The peripheral blood smear will be reviewed by a pathologist because reliance cannot be placed on automated differential blood counts. For assessment of the bone marrow, examination of an aspirate is preferred. Trephine biopsy of the bone marrow will also be obtained because a biopsy allows more bone marrow tissue to be examined and permits identification of clusters of blasts. Biopsy evaluation can also provide a back-up to aspirate findings if the aspirate is dilute, hypocellular, or inaspirable or if spicules are absent from the aspirate sample. Routine cytochemical evaluation (eg, with peroxidase and esterase) will be carried out. Immunophenotyping by flow cytometry (preferred) or immunohistochemistry can be included for determination of cellular lineage determination.

For evaluation of systemic extramedullary disease by radiography, PET-CT is the preferred method [Ohanian 2013], but other methods (eg, MRI, diagnostic CT) may be used, as appropriate. If performed, whole-body FDG PET-CT scanning should be extended from the base of the skull to mid-thigh. Other testing for extramedullary disease (eg, biopsy, cytological assessment of cerebral-spinal fluid or effusions) may be employed

All relevant information required to make each tumor status assessment must be made available for source verification as requested by the study sponsor.

10.3 Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within the specified screening period. On-study tumor assessments should be performed as indicated in Section 7. An end-of-therapy tumor assessment should be performed unless the subject already has confirmation of TF or DRP ≤8 weeks prior to study drug discontinuation or the medical monitor has waived the requirement. If a subject permanently discontinues treatment prior to objective documentation of AML progression, investigators should continue further follow-up of tumor status with assessments at ~8- to 12-week intervals until disease progression is documented or until the initiation of a new post-study therapy for the subject's AML.

10.4 Definitions of Tumor Remission and Progression

Responses will be categorized as complete remission without minimal residual disease (CR_{MRD-}), complete remission (CR), complete remission with incomplete blood count recovery (CRi), partial remission (PR), disease recurrence or progression (DRP), or treatment failure (TF). In addition, a remission category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize remission status.

The best overall response will be determined. The best overall response is the best on-treatment response from baseline recorded from the start of treatment until DRP or TF. The baseline status will be taken as a reference for determinations of response. The best on-study measurement will be taken as a reference for DRP; the best on-study measurement constitutes the measurement with the least tumor involvement, including the baseline measurement if this is the measurement meeting this criterion.

10.4.1 Complete Remission without Minimal Residual Disease

To satisfy criteria for CR_{MRD-}, all of the following conditions must be attained:

- Leukemia disease status meeting all of the following requirements:
  - Absence of evidence of AML in bone marrow aspirate by flow cytometry
  - <5% bone marrow blasts (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - No blasts in the peripheral blood
  - No blasts with Auer rods
  - No extramedullary disease
- Peripheral blood meeting both of the following requirements:
  - ANC $\geq 1.0 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L

10.4.2 Complete Remission

To satisfy criteria for CR, all of the following conditions must be attained:

- Leukemia disease status meeting all of the following requirements:
  - <5% bone marrow blasts (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - No blasts in the peripheral blood
  - No blasts with Auer rods
  - No extramedullary disease
- Peripheral blood meeting both of the following requirements:
  - ANC $\geq 1.0 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L

10.4.3 Complete Remission with Incomplete Blood Count Recovery

To satisfy criteria for CRi, all of the following conditions must be attained:

- Leukemia disease status meeting all of the following requirements:
  - <5% bone marrow blasts (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - No blasts in the peripheral blood
  - No blasts with Auer rods
  - No extramedullary disease
- Peripheral blood meeting either of the following requirements:
  - ANC $<1.0 \times 10^9$/L
  - Platelet count $<100 \times 10^9$/L

10.4.4 Partial Remission

To satisfy criteria for PR, all of the following conditions must be attained:

- Leukemia disease status meeting either of the following requirements:
  - A ≥50% decrease in bone marrow blasts to 5% to 25% (inclusive) (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - <5% bone marrow blasts but with Auer rods present (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - No blasts in the peripheral blood
  - No new or worsening extramedullary disease

- Peripheral blood meeting both of the following requirements:
  - ANC $\geq 1.0 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L

10.4.5 Treatment Failure

The occurrence of any of the following events indicates TF:

- In a subject without DRP, inability to qualify for a CR_{MRD-}. CR, CRi, or PR by 8 weeks from start of study therapy
- In a subject without a CR_{MRD-}. CR, CRi, PR, or DRP, permanent cessation of study therapy due to an AE
- In a subject without a CR_{MRD-}. CR, CRi, PR, or DRP, death from any cause

10.4.6 Disease Relapse or Progression

The occurrence of any of the following events indicates DRP:

- Reappearance of bone marrow blasts to >5% in a subject who had experienced a CR or CRi
- Reappearance of blasts in the peripheral blood in a subject who had experienced a CR, CRi, or PR
- An absolute 20% increase in bone marrow blasts to >25% (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules) in a subject who had experienced a PR
- Development of new or worsening existing extramedullary disease

Reoccurrence or worsening of MRD, as assessed by flow cytometry, will not be considered in the definition of DRP, but will be recorded.

10.4.7 Nonevaluable

In a subject who does not have TF or DRP, the occurrence of any of the following conditions indicates a remission status of NE:

- Bone marrow aspiration/biopsy data are inadequate or missing
- Peripheral blood data are inadequate or missing
- Information for a known site of extramedullary disease is inadequate or missing

11 STATISTICAL CONSIDERATIONS

11.1 Analysis Conventions

11.1.1 Analysis Sets

11.1.1.1 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.

11.1.1.2 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.

11.1.1.3 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.

11.1.2 Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Data will be described and summarized by dosing regimen and time point.

Descriptive summaries for continuous variables will contain N (number in population); n (number with data); mean (with standard deviation and confidence intervals [Cis] on the mean); median; minimum; and maximum. Descriptive summaries for categorical variables will include N, n, percentage, and CIs on the percentage.

The baseline value used in each analysis will be the last (most recent) predose value. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the most extreme change from baseline during the study will also be described and summarized. Shift tables or graphical techniques (eg, bar charts, line graphs) may be used when such methods are appropriate and informative.

Data from all study centers will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate. Unless otherwise indicated, CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Unless otherwise specified, statistical testing will be 2-sided at a nominal 0.05 level of significance. Given the exploratory nature of this study, adjustments for multiple comparisons need not be applied.

11.2 Analysis Plan

Details of the statistical analyses will be fully described in a statistical analysis plan to be finalized prior to the analyses.

11.2.1 Subject Disposition and Baseline Characteristics

A listing of all full analysis subjects will be generated to describe study center, subject number, first screening date, first treatment date, dosing regimen, the longest duration of treatment with LAM-003, and the reason for discontinuing LAM-003. Available information on subjects who were screened but not administered study drug may be listed separately. A table will be created summarizing these categories in terms of number and percent for the full analysis set.

Subject baseline characteristics (eg, subject demographics, medical history, disease history, prior therapy, FLT3 mutational status and mutant-to-WT allele ratio, peripheral AML blast count, bone marrow blast percentage, peripheral blood ANC, peripheral blood platelet count, peripheral blood hemoglobin, baseline TLS risk status, etc) will be listed and summarized for the full analysis set.

11.2.2 Study Drug Exposure and Concomitant Medications

11.2.2.1 Treatment Administration and Study Drug Compliance

Descriptive information will be provided regarding the number of doses of LAM-003 prescribed; the number of days of LAM-003 treatment, the number and timing of prescribed LAM-003 dose modifications and interruptions; and the reasons for LAM-003 dose modifications and interruptions.

LAM-003 compliance will be described based on diary information and bottle and tablet counts in terms of the number (%) of study drug doses actually taken relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

11.2.2.2 Prior and Concomitant Medication Use

Prior, concomitant, and postdose medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) into Anatomical Therapeutic-Chemical classification (ATC) codes.

Descriptions of prior medication use will be focused on drugs and regimens used as treatments for AML. As appropriate and if available, information on the sequencing, type, dose, schedule, timing, duration of use, and efficacy of prior regimens will be provided. Descriptions of prior medications used during the screening period will also be provided.

The type and timing of use of concomitant medications and supportive care will be listed and summarized. Information regarding the type and amounts of specific supportive medications or measures (eg, antifungal prophylaxis, antiemetics, TLS prophylaxis, corticosteroid usage) may be described. Use of drugs representing a risk for a CYP3A4-mediated drug-drug interactions may be described.

The number, type, and timing of poststudy treatment regimens for AML will be summarized, characterizing the disposition of all subjects who are eligible for poststudy treatment and those

who are not eligible for poststudy treatment (eg, subjects who are never treated at all, die while on study treatment, are still on study, or are lost to follow-up).

11.2.3 Safety

11.2.3.1 Adverse Events

All AEs will be listed. The focus of AE summarization will be on TEAEs as defined in Section 8.1.4. 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.

AEs will be classified using MedDRA with descriptions by System Organ Class and Preferred Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03 [NCI 2010], 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 relationship of the AE to the study drug will be described based on the categories as outlined in Table 5. As necessary, attributions of "definitely", "probably", or "possibly" related may be aggregated as "related" and attributions of "unlikely" or "unrelated" may be aggregated as "unrelated" to provide a dichotomous description of causal relationships.

Summary tables will be presented to show the number of subjects reporting TEAEs by severity grade and corresponding percentages. A subject who reports multiple TEAEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. AE descriptions will be presented in order of decreasing frequency for System Organ Class, and by decreasing frequency in the overall or total column for a given Preferred Term.

Separate listings and summaries will be prepared for the following types of AEs:

- Study-drug-related AEs
- AEs that are Grade 3, 4, or 5 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- SAEs (with categorization of the primary outcome that results in the AE being considered serious, eg, life-threatening, requiring hospitalization)
- AEs of special interest (see Section 8.1.5)

Separate listings and summaries will be prepared for long-term follow-up safety data (see Section 7).

11.2.3.2 Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data and will be reported using conventional units. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥1 grade in the

period from the first study drug administration to 30 days after the last study drug administration. If baseline data are missing, then any graded 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.

Hematological, serum biochemistry, and coagulation data will be programmatically graded according to CTCAE severity grade, when applicable. 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.

Hematological, serum biochemistry, and coagulation 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, serum biochemistry, and coagulation 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.

Urinalysis data will be summarized in tables. The overall urinalysis assessment will be reported as "Normal" or "Abnormal" with respect to relevant abnormalities based on the reference laboratory ranges provided by the study center. A shift table comparing the urinalysis assessment over the on-study period (ever abnormal) to baseline will be presented with the types of abnormalities tabulated.

11.2.3.3 Vital Signs and Oxygen Saturation

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)

Blood pressure and body temperature data will also be graded according to CTCAE severity grade.

Oxygen saturation data will be reported as percent saturation and values ≤92% and declines from baseline of ≥5% will be categorized programmatically.

Data will be summarized in tables and may be summarized in figures showing values over time or most extreme values on study, if appropriate. The frequencies of subjects with values below, within, and above the normal ranges for vital signs and of subjects with oxygen saturation values ≤92% and for declines from baseline of ≥5% will be summarized in tables. For blood pressure and body temperature data, summary tables will be presented to show the number of subjects by CTCAE severity grade with corresponding percentages. Subjects will be characterized only once for a given parameter, based on their worst severity grade observed during a period of interest (eg, during the study, during a cycle, or at a specific time point).

For vital signs, 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 blood pressure and body temperature, data will also be presented by showing change in CTCAE severity grade from baseline to each time point. 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.

For oxygen saturation, shift tables will be presented showing change in results from baseline to each time point considering categorization of values based on values ≤92% and declines from baseline of ≥5%.

11.2.3.4 Electrocardiography

The overall quantitative and qualitative ECG assessment of heart rate, cardiac intervals, wave form abnormalities, and ectopy will be reported as "Normal" or "Abnormal" with respect to the description of the official ECG reading provided by the CRO performing the ECG analyses. A shift table comparing the ECG assessment over the on-study period (ever abnormal) to baseline will be presented with the types of abnormalities tabulated.

Quantitative ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTc interval) at each time recorded as well as the change from screening will be summarized with descriptive statistics. The QT interval will be corrected by the Fridericia method for purposes of analysis. The following formula will be employed for correction:

- Fridericia: QTcF in msec = $QT/(RR/1000)^{1/3}$

The QTc data obtained by using the Fridericia correction will be categorized separately into the following classifications and summarized by time point:

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

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

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

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

11.2.3.5 Body Weight and Performance Status

Body weight and performance status data will be listed. Data will be summarized in tables.

11.2.3.6 Other Clinical Variables Relating to Safety

Baseline height, baseline calculated body-mass index (in kg/m^2 based on body weight/height^2), baseline serum virology data, and all pregnancy test data will be listed and summarized.

11.2.4 Pharmacokinetics

Pharmacokinetic parameters will be calculated using non-compartmental methods. Only serum concentrations greater than or equal to the validated lower limit of quantitation (LLQ) will be used in the pharmacokinetic analyses. Per-protocol times will be used to calculate mean serum concentrations for graphical displays. Actual blood sampling times will be used in all pharmacokinetic analyses.

The C_{max} and T_{max} will be taken directly from the subject's data. The λ_z will be calculated as the negative of the slope of the terminal log-linear segment of the serum concentration-time curve. The range of data to be used for each subject will be determined by visual inspection of a semi-logarithmic plot of concentration versus time and will comprise any available data points along the elimination phase. Elimination $t_{½}$ will be calculated according to the following equation:

$$t_{½} = \frac{0.693}{\lambda_z}$$

The AUC to the final sample with a concentration ≥LLQ (AUC_{0-t}) will be calculated using the linear trapezoidal method and extrapolated to infinity (AUC_{inf}) using:

$$AUC_{inf} = AUC_{0-t} + \frac{C_{tf}}{\lambda_z}$$

where the final concentration greater than the lower limit of quantitation (C_{tf}) is >LLQ.

CL and V_d will be calculated according to the following respective formulas:

$$CL = \frac{Dose}{AUC_{inf}} \text{ and } V_d = \frac{Dose}{\lambda_z \times AUC_{inf}}$$

Serum concentrations and derived pharmacokinetic parameters will be listed and graphs of individual subject concentrations will be presented on linear and semi-logarithmic axes. Pharmacokinetic data will be summarized using graphical and tabular methods. The data may also be described by baseline variables such as sex, age, weight, and body-mass index.

The relationship between the parameters C_{max}, AUC_{0-inf}, and AUC_{0-24} and the dose may be examined using the power model, ie,

$$P = a \times Dose^b$$

where P represents the parameter and a and b are constants. A value of b of approximately 1 indicates linear pharmacokinetics.

11.2.5 Pharmacodynamics

For each pharmacodynamic variable, the value at each assessment will be described. Changes from baseline to each assessment and the most extreme changes from baseline during the study will be summarized using tabular and graphical methods. The data may also be described by baseline variables such as sex, age, weight, and body-mass index.

As appropriate, changes in the pharmacodynamic parameters will be assessed using paired t-tests or analysis of covariance (ANCOVA) with baseline values as covariates; in these analyses, both changes from baseline to each subsequent time point and most extreme on study changes will be evaluated.

11.2.6 Efficacy Analyses

Tumor control will be documented at each assessment by remission category (eg, CR_{MRD-}, CR, CRi, PR, TF, DRP, or NE, as defined for each response parameter (see Section 10.4), date that response is first documented, and date of tumor progression/failure. MRD status, as assessed by flow cytometry, will be recorded.

11.2.6.1 Categorical Endpoints

OR, CRc, CR_{MRD-}, CR, CRi, and PR rates will be described. In analyses of response rates in the full analysis set, subjects who have best responses of TF, DRP, or NE will be counted as failures. For all analyses of response rates, the relevant CIs will be presented.

11.2.6.2 Time-to-Event Tumor Control and OS Endpoints

For time-to-event endpoints, the following definitions and censoring conventions will be applied:

- TTR will be defined as the interval from the start of study therapy to the first documentation of an objective remission. TTR data will not be censored.
- DOR will be defined as the interval from the first documentation of objective remission to the earlier of the first documentation of DRP or death from any cause. Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anti-AML treatment other than the study treatment or the last time that lack of DRP was objectively documented. Data from subjects who have DRP or die after ≥2 consecutive missing AML assessments will be censored at the last time prior to the missing assessments that lack of DRP was objectively documented.
- EFS will be defined as the interval from start of study therapy to the earliest of the first documentation of TF, DRP, or death from any cause. Data from surviving subjects who do not have TF or DRP will be censored at the earliest of the time of initiation of anti-AML treatment other than the study treatment or the last on-therapy time that lack of TF or DRP was objectively documented. Data from subjects who have DRP or die after ≥2 consecutive missing AML assessments will be censored at the last time prior to the missing assessments that lack of DRP was objectively documented.
- OS will be defined as the interval from the start of study therapy to death from any cause. Data from surviving subjects will be censored at the last time that the subject was known to be alive.

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.

11.2.7 Other Analyses

Using appropriate regression techniques, possible relationships between subject characteristics (eg, sex, race, age, weight, tumor characteristics, dose) and outcome measures (eg, pharmacodynamic and pharmacokinetic parameters) may be assessed. Similarly, associations between outcome measures (eg, relationships between pharmacokinetic and pharmacodynamic parameters) may be evaluated.

11.3 Timing of Analyses

11.3.1 Interim Analyses

No formal interim analyses are planned. As described in Section 2.2, conference calls among the members of the SRC will be conducted periodically to discuss study progress, exchange study information, and 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, the sponsor may collate and summarize available study results during conduct of the study.

11.3.2 Final Analyses

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

11.3.3 Follow-up Analyses

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

11.4 Basis for the Planned Sample Sizes

Sample sizes the cohorts of the study are not based on a specific statistical hypothesis but on experience from similar types of Phase 1 dose-ranging studies in patients with cancer.

In the dose escalation, the cohort sizes of 3 to 6 subjects allow evaluation of regimen safety using a standard definition of MTD (ie, a starting dose associated with DLT in <17% of subjects during the first cycle of therapy). Based on the planned 3+3 dose-escalation scheme, Table 9 shows the probability of escalating to the next dose level or proceeding to the next cohort, based on the true rate of DLT at the current dose level.

Table 9: 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.

12 STUDY ADMINISTRATION AND RESPONSIBILITIES

12.1 General Investigator Responsibilities

The principal investigator must ensure that:

- He or she will personally conduct or supervise the study.
- His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the relevant Study Personnel documents.
- The study is conducted according to the protocol and all applicable regulations.
- The protection of each subject's rights and welfare is maintained.
- Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting study procedures. If a subject withdraws permission to use protected health information, the investigator will obtain a written request from the subject and will ensure that no further data be collected from the subject.
- The consent process is conducted in compliance with all applicable regulations and privacy acts.
- The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
- Any amendment to the protocol is submitted promptly to the IRB/IEC.
- Any significant protocol deviations are reported to the medical monitor, the sponsor, and the IRB/IEC according to the guidelines at each study center.
- eCRF pages are completed in a timely fashion.
- All SAEs are reported to the sponsor (or designee) within 24 hours of knowledge and to the IRB/IEC per IRB/IEC requirements.
- All safety reports are submitted promptly to the IRB/IEC.

12.2 Protocol Compliance

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

12.3 Compliance with Ethical and Regulatory Guidelines

The investigator will ensure that this study is conducted in accordance with ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a US IND, the investigator will ensure adherence to the basic principles of GCP as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998.

This study is also subject to and will be conducted in accordance with 21 CFR, Part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

Because this is a "covered" clinical trial, the investigator will ensure adherence to 21 CFR, Part 54, 1998; a covered clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator in the trial. The investigator or sub-investigator agrees to notify the sponsor of any change in reportable financial interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

12.4 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB/IEC. Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter from the IRB/IEC to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval. A signed protocol approval page, a letter confirming IRB/IEC approval of the protocol and informed consent, and a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations must be forwarded to the sponsor before screening subjects for the study. Additionally, study centers must forward a signed Form FDA 1572 (Investigator Obligation Form) to the sponsor before screening subjects for study enrollment.

Any modifications or amendments made to the protocol or informed consent document after receipt of the initial IRB/IEC approval must also be submitted to the IRB/IEC for approval before implementation. Only changes necessary to eliminate apparent immediate hazards to the subjects may be initiated prior to IRB/IEC approval. In that event, the investigator must notify the IRB/IEC, the medical monitor, and the sponsor in writing within 5 working days after implementation. If a change to the protocol in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by the sponsor before the amendment may take effect. Additionally, under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised informed consent document confirming willingness to remain in the trial.

The investigator shall submit a progress report at least once yearly to the IRB/IEC, and must provide a copy to the sponsor. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC and to the sponsor. This report should include the dates of initiation and completion of the trial, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of subjects evaluated, the number of subjects who discontinued (and the reasons for discontinuation), the number of subjects who completed the trial, and the results of the trial,

including a description of any AEs. The sponsor will assist the investigator in the preparation of this report, as needed.

12.5 Informed Consent

The investigator, or a designee (designee must be listed in the relevant in the relevant study personnel documents), must explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in 21 CFR Part 50 and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before enrollment into this study. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

A copy of the IRB/IEC-approved informed consent must be forwarded to the sponsor or designee for regulatory purposes.

12.6 Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this study drug, the investigator agrees to allow the IRB/IEC, representatives of the sponsor and its designated agents, and authorized employees of appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the study center records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of clinical, laboratory, ECG, radiology, pathology, and/or other test results when requested by the sponsor. A statement to this effect will be included in the informed consent and a permission form authorizing the use of protected health information will also be included.

In accordance with local and national subject privacy regulations, the investigator or designee must explain to each subject that in order to evaluate study results, the subject's protected health information obtained during the study may be shared with IRB/IECs, the sponsor and its designees, and regulatory agencies. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results. The sponsor will only use or disclose the subject's protected health information as defined in the informed consent document.

The investigator must assure that each subject's anonymity will be strictly maintained and that each subject's identity is protected from unauthorized parties. Only subject initials, date of birth, and an identification code (but no subject names) should be recorded on any form or biological sample submitted to the IRB/IEC, to the sponsor or its designees (eg, laboratories), or to regulatory authorities. However, sufficient information must be retained at the study center to permit sample data and data in the database to be connected with the unique subject number assigned to each study participant.

The investigator agrees that all information received from the sponsor, including but not limited to the study drug, the investigator brochure, this protocol, the eCRFs, and any other study

information remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

12.7 Study Files and Retention of Records and Biological Samples

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified by the IRB/IEC, representatives of the sponsor and its designated agents, and authorized employees of appropriate regulatory agencies. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, the IRB/IEC and governmental approval with correspondence, signed informed consent documents, drug accountability records, staff curriculum vitae and authorization forms (eg, Form FDA 1572), and other appropriate documents and correspondence pertaining to the conduct of the study.

The required source data referenced in the monitoring plan for the study should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that the subject meets eligibility criteria, eg, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Participation in trial (including trial number)
- Trial discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug (including relevant drug dispensing information)
- Record of all AEs and other safety parameters (including start and end date, causality and intensity)
- Concomitant medications (including start and end date and dose if relevant dose changes occur)
- Date of trial completion and reason for discontinuation, if applicable

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, the United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years

after the investigation is discontinued and regulatory authorities have been notified or for 15 years, whichever is longer. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor and obtain written approval from the sponsor before destroying any clinical study records. The investigator will promptly notify the sponsor in the event of accidental loss or destruction of any study records. The sponsor will inform the investigator of the date that study records may be destroyed or returned to the sponsor.

The sponsor must be notified in advance and must provide express written approval of any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party.

If the investigator cannot guarantee this archiving requirement at the study center for any of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the study center so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the study center.

Biological samples retained by the investigator will be stored and maintained by the investigator until notification is received from the sponsor that the retained samples and records no longer need to be retained. The investigator must obtain written permission from the sponsor before disposing of any retained samples. The investigator should promptly notify the sponsor in the event of accidental loss or destruction of any study samples. With the permission of the sponsor, the retained samples may be transferred to an acceptable designee, such as another investigator, another institution, a contract laboratory, a contract storage site, or to the sponsor.

12.8 Subject Screening Log

The investigator must keep a record that lists all subjects who signed the informed consent (including those who did not undergo screening). For those subjects who declined to participate or were subsequently excluded from enrollment, the reasons for not enrolling in the study must be described.

12.9 Modifications of the Protocol or Informed Consent Documents

Protocol modifications, except those intended to reduce immediate risk to study participants, will be made only by the sponsor. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Except as noted in Section 12.4, IRB/IEC approval must be obtained before changes can be implemented.

Informed consent documents cannot be changed without prior approval by the sponsor and the study center IRB/IEC.

12.10 Case Report Forms

Authorized study center personnel will complete eCRFs designed for this study according to the completion guidelines that will be provided. An eCRF is required and must be completed for each enrolled subject, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, study center charts, or other study-specific source documents). The investigator will ensure that the eCRFs

are accurate, complete, legible, and completed in a timely fashion after each subject's visit. The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed. As required by the protocol, eCRFs should also be completed for those subjects who fail to complete the study (even during the screening period). If a subject withdraws from the study, the reason must be noted on the eCRF and thorough efforts should be made to clearly document outcome.

The eCRFs for this study will exist within a web-based electronic data capture (EDC) system. After the investigator or the investigator's designees (eg, research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

The eCRF must be completed and signed by the principal investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This signature serves to attest that the information contained in the eCRF is true.

12.11 Study Drug Accountability

The disposition of all investigational LAM-003 should be documented from the time of receipt at the study center through subject administration. An investigational drug accountability log must be maintained for drug accountability. It is acceptable to use a protocol-specific form or a study center form that captures the relevant information. Within the drug accountability log, the responsible study center personnel must maintain accurate records of the receipt of all LAM-003 shipped by the sponsor (or its designee), including, but not limited to, the date received, lot number, amount received, pertinent details about the condition of the study drug upon receipt based on visual inspection, and the disposition of the drug (eg, to storage). If a LAM-003 drug shipment arrives damaged, or if there are any other complaints relating specifically to the drug, a product complaint should be emailed to the sponsor or the sponsor's representative. LAM-003 accountability records must also be maintained that include the subject number to whom the study drug was administered and the date, quantity and lot number of the LAM-003 administered.

Study personnel must ensure that LAM-003 is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or study center personnel supply LAM-003 to other investigators, subjects, or clinics, or allow the study drug to be used other than as directed by this protocol without the prior authorization from the sponsor.

Depending upon the decision of the sponsor, remaining unused LAM-003 supply will be returned to the sponsor or its designee after the study is completed or will be discarded or destroyed at the study center. After investigational product accountability has been performed, LAM-003 may be returned or destroyed on an ongoing basis during the study if appropriate. If the study drug is discarded or destroyed at the study center, standard institutional policy should be followed. At study initiation, the monitor will evaluate the study center's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with sponsor requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study center will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the study center cannot meet sponsor

requirements for disposal, arrangements will be made between the study center and the sponsor or its representative for destruction or return of unused study drug supplies.

All study drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study. Study drug accountability records must be readily available for inspection by the study monitor or other representatives of the sponsor or by regulatory authorities.

12.12 Monitoring

Representatives of the sponsor or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and study center staff as well as any appropriate communications by mail, fax, email, or telephone. The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data.

In accordance with GCP, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.13 Inspections

The source documents for this trial must be made available to appropriately qualified personnel from the sponsor or its representatives, to IRB/IECs, and to regulatory authority or health authority inspectors as a part of their responsibility to protect human subjects in research. The investigator agrees to provide access to records, facilities, and personnel for the effective conduct of any inspection or audit to representatives of the sponsor and regulatory agencies. It is important that the investigator and relevant institutional personnel are available during monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor immediately.

12.14 Data Management

Electronic data capture will be used to enter study data into eCRFs and to transfer the data into a study-specific electronic database. During the data collection process, automated quality assurance programs will be used to identify missing data, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be forwarded to the investigative study center for resolution. As appropriate, eCRFs, listings, tables, and SAS datasets will be provided to the study centers for review.

Quality assurance and quality control systems will be implemented and maintained according to written standard operating procedures to ensure that the data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Data collection and storage systems will provide audit trail, security mechanisms, and electronic signature capabilities that meet the requirements of FDA Title 21 of CFR Part 11 regarding electronic records and electronic signatures.

Data security will be controlled through appropriate and specific restriction of access only to data and systems required by individual users to accomplish their roles in the data management process. Individual login and password protections will be employed at study centers and at the sponsor or its designee. The database will exist on physically secured servers. Data backups will be done regularly and will be stored in separate facilities. Printed documents relating to the study will be secured when not under review.

12.15 Clinical Trial Insurance

The sponsor will secure clinical trial insurance. An insurance certificate will be made available to the participating study centers before study initiation.

12.16 Communications with Regulatory Authorities

The sponsor (or its designee) will assume responsibility for interactions with the FDA and any other relevant regulatory authorities. The sponsor will maintain an IND for LAM-003 in support of the study in the US and will maintain similar regulatory applications with other regulatory authorities as required for conduct of the study. In fulfilling these responsibilities, the sponsor (or a designee) will collect and assemble all required regulatory documents (eg, Form FDA 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. The sponsor (or a designee) will also assume responsibility for AE reporting to regulatory authorities (as described in Section 8.8).

12.17 Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and to ensure meeting the requirement of the International Committee of Medical Journal Editors (ICMJE) as a condition of consideration for publication of study results, the sponsor will register this protocol at the ClinicalTrials.gov website (or equivalent). If the protocol is registered at ClinicalTrials.gov, the sponsor will appropriately update the information at the website relating to study design and conduct during the course of the study. In order to facilitate this process, investigators will need to supply the sponsor with appropriate contact information for study center personnel.

12.18 Study Reporting and Publication

The sponsor may make information obtained during this study available in order to further the scientific or business needs of the company or as required by law or regulation. In this regard, the sponsor may provide study information to private or public organizations (eg, business partners, collaborators, consultants, CROs, investors, other physicians who are conducting similar studies, funding organizations, regulatory authorities, or other government authorities). The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis.

The sponsor will prepare a clinical study report for submission to relevant regulatory agencies. The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases, as appropriate.

The sponsor intends that the data from this study will be presented and published. Because the study will ultimately part of a multicenter clinical trial, data from all study centers will be pooled and analyzed for a primary publication of the study results. The sponsor will coordinate and prepare this primary publication. The investigator agrees that the primary publication, which will be coordinated by the sponsor, will be the first publication to present the pooled study results. Other ancillary publications or presentations relating to the pooled data from this study may be suggested by the investigator, but can only be published with the express consent of the sponsor and the other investigators; such ancillary publications will also be coordinated by the sponsor.

After the primary publication, or if the primary publication is not published within 2 years of termination of the study, the investigator may freely publish or present the results of his or her work conducted under the clinical trial agreement, subject to providing the sponsor with the opportunity to review the contents of any proposed presentation, abstract, or publication about such work, including any results of this study, in advance of any presentation or submission for publication. Within that advance notice period, the sponsor may review the proposed publication to identify patentable subject matter and/or any inadvertent disclosure of its confidential information, which must be redacted from any final publication or presentation. If necessary, to permit the preparation and filing of patent applications, the sponsor may elect an additional review period. The durations of the review periods will be specified in contractual agreements between each study center and the sponsor.

In most cases, the principal investigators at the study centers with the highest accruals of eligible subjects and/or who have provided significant intellectual input into the study design, shall be listed as lead or senior authors on publications and presentations of study results. Sponsor clinical personnel, lead statistician, scientific personnel, or other staff members meeting the requirements for authorship may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and the sponsor.

12.19 Study Discontinuation

Both the investigator and the sponsor reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. The investigator will be responsible for notifying the relevant study center IRB/IEC. The sponsor will be responsible for notifying the appropriate regulatory authorities. In terminating the study, the investigator and the sponsor will assure that adequate consideration is given to the protection of the subjects' interests. As directed by the sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

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14 APPENDICES

14.1 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference: [Oken 1982]

14.2 Cockcroft-Gault Method for Estimating Creatinine Clearance

Formulas for calculating the estimated creatinine clearance (eC_{cr}) are provided below. The formula appropriate to the units in which serum creatinine was measured and the subject's sex should be used.

Cockcroft-Gault Formulas for Calculating Estimated Creatinine Clearance		
Serum Creatinine Units	**Sex**	**Formula**
mg/dL	Males	eCl_{CR} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.0}{72 \times \text{subject serum creatinine [mg/dl]}}$
	Females	eCl_{CR} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 0.85}{72 \times \text{subject serum creatinine [mg/dl]}}$
µM/dL	Males	eCl_{CR} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.23}{\text{Subject serum creatinine [µM/dL]}}$
	Females	eCl_{CR} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.04}{\text{Subject serum creatinine [µM/dL]}}$

Abbreviation: eCl_{CR}=estimated creatinine clearance

14.3 Substrates of CYP3A4

Alfentanil (Alfenta) [b]	Dexamethasone (Decadron) [a]	Itraconazole (Sporanox)	Rilpivirine [c]
Alfuzosin (Uroxatral) [a]	Dihydroergotamine	Ixabepilone (Ixempra)	Riociguat
Almotriptan (Axert) [a]	Diltiazem (Cardizem)	Ixabepilone (Ixempra)	Ritonavir (Norvir)
Alprazolam (Xanax) [a] [c]	Disopyramide (Norpace) [a]	Ketoconazole (Nizoral)	Rivaroxaban [c]
Amiodarone (Cordarone) [a]	Docetaxel (Taxotere)	Lapatinib (Tykerb)	Saquinavir (Invirase) [b]
Amlodipine (Norvasc)	Donepezil (Aricept)	Levomethadyl (Orlaam)	Saxagliptin (Onglyza) [a]
Apixaban	Doxorubicin (Adriamycin)	Lomitapide [a] [b]	Sibutramine (Meridia)
Aprepitant (Emend) [c]	Dronedarone [b]	Lopinavir (Kaletra)	Sildenafil (Viagra) [a] [b]
Astemizole	Droperidol	Loratadine (Claritin)	Simvastatin (Zocor) [a] [b]
Atazanavir (Reyataz)	Dutasteride (Avodart)	Lovastatin (Mevacor) [a] [b]	Sirolimus (Rapamune) [b]
Atorvastatin (Lipitor) [a] [c]	Ebastine (Kestine) [b]	Lurasidone [b]	Sitagliptin (Janumet) [a]
Avanafil [a] [b]	Efavirenz (Sustiva)	Maraviroc (Selzentry) [b]	Solifenacin (Vesicare)
Axitinib (Inlyta) [a]	Eletriptan (Relpax) [b]	Mefloquine (Lariam)	Sorafenib
Bedaquiline (Sirturo) [a]	Eliglustat [c]Elvitegravir	Methylprednisolone [a]	(Nexavar)Sufentanil
Bepridil (Vascor)	(Stribild)	Midazolam (Versed) [a] [b]	(Sufenta)
Bexarotene (Targretin)	Eplerenone (Inspra) [a] [b]	Mifepristone (Mifeprex) [a]	Sunitinib (Sutent)
Bosentan (Tracleer)	Ergotamine (Ergomar) [a] [a]	Modafinil (Provigil)	Suvorexant (Belsomra)
Brexpiprazole (Rexulti)	Erlotinib	Naloxegol [b]	Tacrolimus (Prograf) [a] [b]
Bromocriptine (Parlodel)	(Tarceva)Erythromycin	Nefazodone	Tadalafil (Cialis) [a] [c]
Budesonide (Entocort) [a] [b]	Estazolam (ProSom)	Nevirapine (Viramune)	Tamoxifen (Nolvadex)
Buprenorphine (Subutex)	Eszopiclone (Lunesta)	Nicardipine (Cardene)	Tamsulosin (Flomax)
Bupropion (Buspar, Zyban,	Ethinyl Estradiol	Nifedipine (Adalat)	Teniposide (Vumon)
Wellbutrin, Voxra)	Ethosuximide (Zarontin)	Nimodipine (Nimotop)	Testosterone
Buspirone	Etoposide (Vepesid)	Nisoldipine (Sular) [b]	Testosterone
Cabazitaxel (Jevtana)	Etravirine (Intelence)	Nitrendipine (Baypress)	Tiagabine (Gabitril)
Carbamazepine (eg, Tegretol) [a]	Everolimus (Afinitor) [b]	Oxycodone (Percodan) [a]	Ticagrelor [b]
Cevimeline (Evoxac)	Exemestane (Aromasin)	Paclitaxel (Taxol)	Tinidazole (Tindamax)
Cilostazol (Pletal)	Felodipine (Plendil) [b]	Paricalcitol	Tipranavir (Aptivus) [b]
Cisapride (Propulsid)	Fentanyl (Sublimaze) [a]	(Zemplar)Paritaprevir (in	Tofacitinib
Clarithromycin (Biaxin)	Finasteride (Proscar)	Technivie)	Tolvaptan [b]
Clonazepam (Klonopin)	Flurazepam (Dalmane)	Pimozide (Orap) [a]	Topiramate (Topamax)
Clopidogrel (Plavix)	Fluticasone (Flovent) [a]	Praziquantel (Biltricide)	Triazolam (Halcion) [a] [b]
Colchicine [a] [c]	Fosamprenavir (Lexiva)	Prednisolone	Vardenafil (Levitra) [a] [b]
Conivaptan [b]	Fosamprenavir (Lexiva)	Prednisone	Vemurafenib (Zelboraf)
Cyclophosphamide (Cytoxan)	Galantamine (Reminyl)	Propoxyphene (Darvon)	Verapamil (Calan)
Cyclosporine (Neoral) [a]	Gefitinib (Iressa)	Quazepam (Doral)	Vilazodone (Viibryd)
Dabrafenib	Granisetron (Kytril)	Quetiapine (Seroquel) [b]	Vinblastine (Velbane) [a]
Daclatasvir (Daklinza)	Halofantrine (Halfan)	Quinacrine	Vincristine (Oncovin) [a]
Dapsone (Avlosulfon)	Ibrutinib (Imbruvica) [b]	Quinidine [a]	Ziprasidone (Geodon)
Darifenacin [b]	Ifosfamide (Ifex)	Quinine	Zolpidem (Ambien)
Darunavir (Prezista) [b]	Imatinib (Gleevec)	Ranolazine (Ranexa) [a]	Zonisamide (Zonegran)
Dasatinib (Sprycel) [b]	Indinavir (Crixivan) [b]	Regorafenib (Stivarga)	Zopiclone (Imovane)
Delavirdine (Rescriptor)	Irinotecan (Camptosar) [a]	Repaglinide (Prandin) [a]	
	Isradipine (DynaCirc)	Rifabutin (Rimactane) [a]	

a. CYP3A4 substrates producing potentially serious toxicity when combined with CYP3A4 inhibitors

b. Sensitive substrates of CYP3A4 (demonstrate an increase in AUC of ≥5-fold with strong CYP3A4 inhibitors)

c. Moderately sensitive substrates of CYP3A4 (demonstrate an increase in AUC of ≥2- to <5-fold with strong CYP3A4 inhibitors)

References: [Horn 2015, FDA 2016]
Abbreviation: CYP=cytochrome P450 enzyme

14.4 Strong Inhibitors and Inducers of CYP3A4

Effect on CYP3A	Drug
Strong CYP3A Inhibitors	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavi), grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole
Strong CYP3A Inducers	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

Reference: [FDA 2017]
Abbreviation: CYP=cytochrome P450 enzyme

14.5 Drugs Known to Prolong the Cardiac QT Interval

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox®	Anticancer	Cancer (leukemia)
Astemizole (Removed from Market)	Hismanal®	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection
Bepridil (Removed from Market)	Vascor®	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen®	Antimalarial	Malaria
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection
Cisapride (Removed from Market)	Propulsid®	Gastrointestinal stimulant	Increase gastrointestinal motility
Citalopram	Celexa®, Cipramil®	Antidepressant, selective serotonin reuptake inhibitor	Depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace®	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn®	Antiarrhythmic	Abnormal heart rhythm
Domperidone (Only on Non-US Market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antinausea	Nausea, vomiting
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq®	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S.®, Robimycin®, Emycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection, increase gastrointestinal motility

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	Antidepressant, selective serotonin reuptake inhibitor	Depression (major), anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Diflucan®, Trican®	Antifungal	Fungal infection
Gatifloxacin (Removed from Market)	Tequin®	Antibiotic	Bacterial infection
Grepafloxacin	Raxar®	Antibiotic	Bacterial infection
Halofantrine	Halfan®	Antimalarial	Malaria
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic	Schizophrenia, agitation
Ibutilide	Corvert®	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial infection
Levomepromazine (Only on Non-US Market)	Nosinan®, Nozinan®, Levoprome®	Antipsychotic	Schizophrenia
Levomethadyl (Removed from Market)	Orlaam®	Opioid agonist	Narcotic dependence
Mesoridazine (Removed from Market)	Serentil®	Antipsychotic	Schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin®	Antineoplastic Agent	Cancer
Papaverine HCl	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam®	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap®	Antipsychotic	Tourette's Disorder

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Probucol (Removed from Market)	Lorelco®	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic	Abnormal heart rhythm
Roxithromycin (Only on Non-US Market)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®	Antibiotic	Bacterial infection
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin (Removed from Market)	Zagam®	Antibiotic	Bacterial infection
Sulpiride (Only on Non-US Market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Antipsychotic, atypical	Schizophrenia
Terfenadine (Removed from Market)	Seldane®	Antihistamine	Allergic rhinitis
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa®	Anticancer	Cancer (thyroid)

Note: Includes those drugs known to prolong the cardiac QT interval [Woosley 2016].

14.6 Summary of Changes to Protocol – Amended Version 2

14.6.1 Overview of Changes

Modifications from Version 1 to Version 2 of the protocol included the following:

- The title of the study was simplified prior to listing of the study at clinicaltrials.gov.
- The LAM-003 chemical name was changed to follow the naming convention of the International Union of Pure and Applied Chemistry.
- Figure 3 (LAM-003 In Vitro Efficacy in Cancer Cells from a Patient with Gilteritinib- and Sorafenib-Resistant AML) was updated to match the final figure that was included in the investigator brochure and IND.
- The study design was revised to remove Part 2 (cohort expansion) based on the FDA recommendation not to conduct the cohort expansion portion of the study until additional information is available to develop an appropriate plan for assessing the long-term safety of LAM-003. All references to Part 2 of the study were removed from the protocol consistent with the change in the study design.
- The efficacy endpoints were expanded to include the categories of and definitions for complete remission without minimal residual disease (CR_{MRD}) and composite complete remission (CRc), as recommended by FDA, and to remove references to red blood cell (RBC) transfusions as a component of response (for consistency with 2017 European Leukemia Net [ELN] proposals for response criteria).
- The inclusion and exclusion criteria were modified as follows:
    - Inclusion Criterion 9 was modified to change the allowable value for estimated creatinine clearance (eCl_{CR}) from >50 mL/minute to >60 mL/minute, as recommended by FDA based on observations in nonclinical studies (renal excretion and increases in serum creatinine levels) and an event of renal failure in the earlier study of LAM-003A in subjects with solid tumors.
    - Exclusion Criterion 4 was modified to clarify that only subjects with Grade >1 proliferative or nonproliferative retinopathy would be excluded at the request of the consulting ophthalmologist for the study.
- The following changes to the dose levels of LAM-003 and recommendations for dose modifications of LAM-003 were made based on FDA review of Version 1 of the protocol:
    - The dose levels of LAM-003 after Dose Level 1 were revised to reflect 1.5-fold increases in dose (rather than 1.75-fold increments), resulting in a maximum dose level of <480 mg/day, which was the MTD in the earlier study of LAM-003A in subjects with solid tumors.
    - The previous dose modification recommendations for LAM-003 were revised to 1) make dose modifications for toxicities mandatory, 2) ensure that dose reductions are done in accordance with the protocol-specified dose levels, 3) state that subjects who cannot tolerate LAM-003 after 2 progressive dose reductions or a decrease to Dose Level -2 (50 mg/day) should be discontinued from study drug therapy, 4) clarify that subjects

whose dose is de-escalated are not eligible for dose re-escalation if they have experienced Grade >2 toxicities at the current dose level, 5) clarify resumption of LAM-003 therapy in subjects who experience adverse events (AEs) that preclude resumption of therapy by Day 29, and 6) provide additional dose-modification guidelines for subjects who experience treatment-emergent visual toxicities.

- Additional information on the rationale for exploring the one-per-day (QD) and twice-per-day (BID) dosing regimens was provided.
- At the request of the FDA, hematologic toxicity (Grade 4) neutropenia was added as a DLT and the DLT criteria for visual disturbances and TLS were revised.
- At the request of the FDA, the previous guidance on the use of hematopoietic agents and other growth factors as supportive care was revised to conform to National Comprehensive Cancer Network (NCCN) guidelines.
- As requested by the FDA, specific guidance on ophthalmologic follow-up (including appropriate assessment methods) and resumption of LAM-003 therapy in subjects who experience dose-limiting visual toxicity was added.
- As requested by the FDA, additional monitoring for TLS, including assessment of vital signs, AEs, and laboratory studies (hematology and serum chemistry), was added.
- As requested by the FDA, the reasons for treatment discontinuation were clarified and expanded.

14.6.2 Specific Changes

In preparing Amended Version 2 of the protocol document, the following specific changes were made. Explanations of the changes are provided in italics as "***Changes/Rationale***". Inserted text is indicated by double-underlining. Deleted text is indicated by ~~strikeout~~. Revisions to the synopsis are not described. Changes to protocol versions, dates, the list of abbreviations and definitions of terms, and minor typographical or syntax corrections are not indicated.

Changes to: Title Page, AI Therapeutics Project Personnel, Principal Investigator Approval Page

Changes/Rationale: The title of the study has been simplified prior to listing of the study at clinicaltrials.gov.

Protocol Title	A Phase 1 Dose-Escalation ~~and Cohort-Expansion~~ Study of ~~the Heat Shock Protein 90 Inhibitor,~~ LAM-003~~,~~ in Patients with Acute Myeloid Leukemia

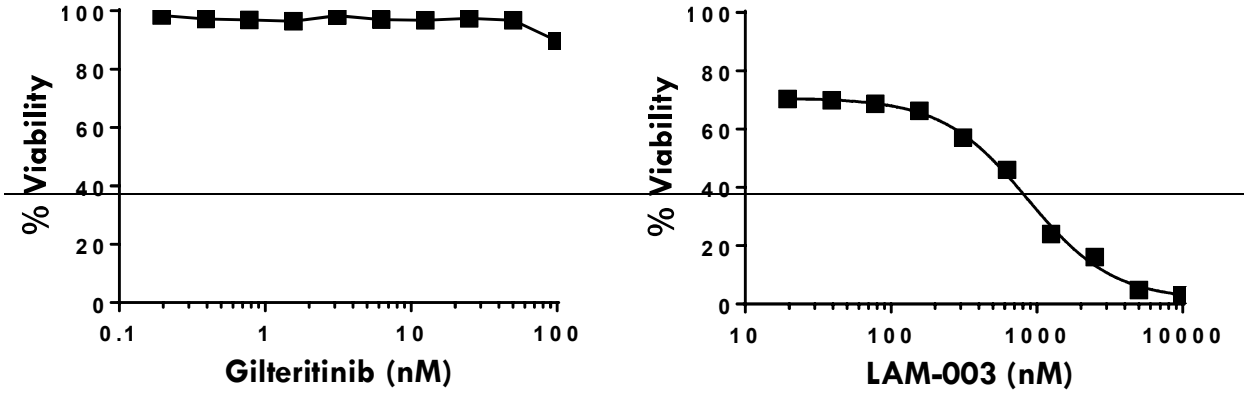
Changes to: Section 1 INTRODUCTION, 1.4.2 Chemistry

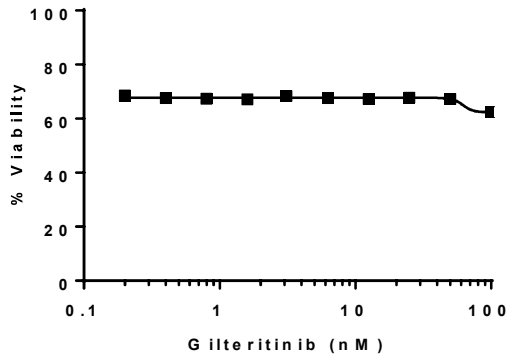
Changes/Rationale: The LAM-003 chemical name was changed to follow the naming convention of the International Union of Pure and Applied Chemistry.

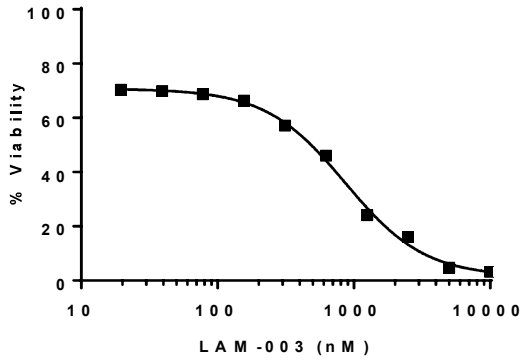
LAM-003 has the chemical name of [(1S)-2-[4-[2-[6-amino-8-[(6-bromo-1,3-benzodioxol-5-yl)sulfanyl]purin-9-yl]ethyl]-1-piperidyl]-1-methyl-2-oxo-ethyl] (2S)-2-aminopropanoate mono-mesylate, mono-hydrate]~~(2S)-1-[4-(2-{6-amino-8-[(6-bromo-1,3-benzodioxol-5-yl) sulfanyl]-9H-purin-9-yl}ethyl)piperidin-1-yl]-1-oxopropan-2-yl L-alaninate mono-mesylate, mono-hydrate)~~.

Changes to: Section 1 INTRODUCTION, 1.4.3 Nonclinical Experience, 1.4.3.1 Efficacy Pharmacology, 1.4.3.1.1 In Vitro Studies, Figure 3 (LAM-003 In Vitro Efficacy in Cancer Cells from a Patient with Gilteritinib- and Sorafenib-Resistant AML)

Changes/Rationale: Figure 3 was updated to match the final figure that was in included in the investigator brochure and IND.







Changes to: Section 2 STUDY DESIGN AND CONDUCT, 2.1 Study Design and 2.3 Rationale for Study Design

Changes/Rationale: The study design was revised to remove Part 2 (cohort expansion) of the study in accordance with FDA guidance not to conduct Part 2 study until additional information was available from the Part 1 (dose escalation).

2.1 Study Design

~~This clinical trial is a Phase 1 study of the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of LAM-003. The study will be conducted in 2 parts comprising an initial dose escalation followed by a subsequent cohort expansion.~~

~~2.1.1 Part 1 Dose Escalation~~

This clinical trial is a Phase 1 study evaluating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of LAM-003 across ~~This portion of the study will evaluate the safety and pharmacology of~~ a range of LAM-003 dose levels when administered to subjects with previously treated relapsed or refractory FLT3-ITD-mutant AML. Subjects will self-administer oral LAM-003 QD or BID continuously in repeated 28-day cycles. Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher dose levels of LAM-003 using a standard 3+3 dose-escalation design. Based on the pattern of DLTs observed in Cycle 1, escalation will proceed to define an MTD and a recommended dosing regimen (RDR) that may be at the MTD or a lower dose within the tolerable dose range.

2.1.2 Part 2 Cohort Expansion

~~This portion of the study will further explore the safety, pharmacology, and clinical activity of LAM-003 monotherapy in patients with FLT3-ITD-mutant AML. Study subjects will self-administer LAM-003 orally using the RDR derived from Part 1 of the study. The planned sample size will be based on a futility analysis testing if there is antitumor activity sufficient to warrant further development of LAM-003 for FLT3-ITD-mutant AML. A continuous reassessment of safety will be used to confirm the selection of the RDR.~~

2.3 Rationale for Study Design

The study has been designed to provide critical dosing, safety, pharmacokinetic, pharmacodynamic, and early efficacy data in support of future clinical development of LAM-003 in larger clinical trials.

~~In Part 1 of the study, d~~Dose-ranging in cohorts of 3 to 6 subjects using a 3+3 design is consistent with usual oncologic drug development in the Phase 1 evaluation of various types of anticancer agents; this method provides efficient dose escalation while limiting the number of subjects who are exposed to excessively toxic doses of study drug.

~~In Part 2 of the study, enrollment of an expansion cohort provides confirmation of starting dose selection and permits evaluations of drug safety and pharmacology while generating preliminary observations regarding drug activity. The intent is to confirm safety and seek an efficacy signal but to limit total enrollment using a continuous reassessment of safety and a futility analysis of efficacy to protect subjects against excessive drug toxicity or insufficient drug activity.~~

Changes to: Section 3 STUDY OBJECTIVES, 3.1 Primary Objectives

Changes/Rationale: The primary objectives were revised to remove the objectives for Part 2 (cohort expansion) of the study consistent with the revised study design.

3.1 Primary Objectives~~s~~

~~**3.1.1 Part 1 (Dose Escalation)**~~

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

~~**3.1.2 Part 2 (Cohort Expansion)**~~

- ~~To evaluate the antitumor activity of LAM-003 in subjects with FLT3-ITD-mutant AML~~

Changes to: Section 4 STUDY ENDPOINTS, 4.1 Primary Endpoints

Changes/Rationale: The primary endpoints were revised to remove the primary endpoint for Part 2 (cohort expansion) of the study consistent with the revised study design.

4.1 Primary Endpoints

~~**4.1.1 Part 1 (Dose Escalation)**~~

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

~~**4.1.2 Part 2 (Cohort Expansion)**~~

- ~~Composite complete remission (CRc), defined as complete remission (CR) or complete remission with incomplete count recovery (CRi)~~

Changes to: Section 4 STUDY ENDPOINTS, 4.2.3 Antitumor Activity and Survival

Changes/Rationale: The efficacy endpoints categories were expanded and the definitions provided for CR_{MRD} and CRc, as recommended by FDA, and references to RBC transfusions as a component of response were removed (for consistency with 2017 ELN proposals for response criteria).

Efficacy will be evaluated using standard remission and progression criteria [Cheson 2003, Döhner 2017] as adapted for use in the context of protocol therapy for relapsed or refractory

AML. ~~Besides the Part 2 primary endpoint (defined in Section 4.1.2 above), other e~~ 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 ~~all~~ both of the following criteria: ANC $\geq 1.0 \times 10^9$/L and~~,~~ platelet count $\geq 100 \times 10^9$/L~~, and no requirement for red blood cell transfusions to maintain hemoglobin~~
- 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 ~~any~~ of the following criteria: ANC $< 1.0 \times 10^9$/L or~~,~~ platelet count $< 100 \times 10^9$/L~~, or requirement for red blood cell transfusions to maintain hemoglobin~~
- 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 ~~all~~ both of the following criteria: ANC $\geq 1.0 \times 10^9$/L and~~,~~ platelet count $\geq 100 \times 10^9$/L~~, and no requirement for red blood cell transfusions to maintain hemoglobin~~
- 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

Changes to: Section 4 STUDY ENDPOINTS, 4.3 Rationale for Selection of Endpoints

Changes/Rationale: Paragraph 5 was revised to reflect the addition of CR_{MRD} to the list of efficacy endpoints.

Determinations of the magnitude and duration of changes in AML disease status will be based on well-established remission and progression criteria [Cheson 2003, Döhner 2017] as applied to bone marrow and peripheral blood laboratory measurements (and to radiographic or clinical information in subjects with extramedullary AML). Beyond assessing the ability of the study drug to control cancer growth, AML assessments will also be considered in defining the proper duration of treatment for each study participant. The specific endpoints of overall cancer control

evaluated in this trial are customarily assessed and reported in studies of new therapies in patients with AML. CR_{MRD}, CR, CRi, and PR provide convenient categorization of the magnitude of clinically meaningful reductions in the extent of AML. TTR, DOR, and EFS offer well-established outcome measures that directly evaluate treatment effect, convey important information regarding the rapidity and duration of clinical benefit, can be characterized in all subjects using intention-to-treat principles, and are readily analyzed using statistical methods such as Kaplan-Meier techniques. The 8- to 12-week cadence of tumor assessments is consistent with the expected natural history of remission and progression in relapsed AML, current clinical practice, and the goals of the trial in documenting meaningful LAM-003-mediated AML regression

Changes to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.1 Planned Number of Subjects

Changes/Rationale: The number of subjects who were to be enrolled in Part 2 (cohort expansion) was removed consistent with the revised study design.

5.1 Planned Number of Subjects

~~**5.1.1 Part 1 (Dose Escalation)**~~

The total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all 3 planned starting dose levels and 6 additional subjects are enrolled at the MTD or RDR, as many as 24 subjects could be enrolled. If an additional dose level or an additional schedule (eg, BID) administration is explored in 6 subjects per cohort, as many as 12 additional subjects could be enrolled, bringing the potential sample size to 36 subjects. To allow for the possibility that some subjects may not be fully evaluable, up to 48 subjects may be enrolled.

~~**5.1.2 Part 2 (Cohort Expansion)**~~

~~It is planned that the RDR will be evaluated in 12 evaluable subjects. To allow for the possibility that some subjects may not be fully evaluable, up to 18 subjects may be enrolled.~~

Changes to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.1 Inclusion Criteria

Changes/Rationale: Inclusion criterion 9 was revised to change the allowable value for eCl_{CR} from >50 mL/minute to >60 mL/minute as recommended by FDA based on observations in nonclinical studies (renal excretion and increases in serum creatinine levels) and an event of renal failure in the earlier study of LAM-003A in subjects with solid tumors.

9. Adequate renal function:
    a. Serum creatinine <1.5 × ULN (Grade 1), or
    b. Estimated creatinine clearance (eCl_{CR}) >60 ~~50~~ mL/minute (with eCl_{CR} to be calculated by the Cockcroft-Gault formula [see Appendix 14.2]).

Changes to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.2 Exclusion Criteria

Changes/Rationale: Exclusion criterion 5 was modified to clarify that only subjects with Grade >1 proliferative or nonproliferative retinopathy would be excluded at the request of the consulting ophthalmologist for the study.

4. Ongoing Grade >1 proliferative or nonproliferative retinopathy (eg, due to diabetes mellitus, hypertension, macular degeneration, prematurity, genetic disorder). ***Note: Subjects with resolved retinal tears due to age-related vitreous humor shrinkage are not excluded***.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.1 Premedication, 6.2.1.2 Tumor Lysis Syndrome (TLS) Prophylaxis

Changes/Rationale: The paragraph after the last bulleted point (high risk of TLS) was revised to provide additional guidance on monitoring for TLS, as recommended by FDA.

Subjects must be monitored for TLS during on C1D1 through C1D5 with assessments of vital signs, AEs, and serum chemistry and hematology laboratory studies as described in Section 7. ~~In addition, at the discretion of the investigator, s~~ Study centers may wish to provide additional hydration and in-patient monitoring for TLS, particularly in subjects who are at high risk.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.2 LAM-003 Administration

Changes/Rationale: Additional information related to monitoring for TLS before administration of LAM-003A was added, as recommended by FDA.

In each 28-day cycle, subjects are to self-administer LAM-003 starting on Day 1 and then continuously thereafter (28 total doses/cycle). Subjects should take the study drug at approximately the same time each day, ideally at ~24-hour intervals (eg, ~8AM every day) for the planned QD schedule or at 12-hour intervals (eg, ~8AM and ~8PM every day) if a BID schedule is evaluated. In conjunction with frequent pharmacokinetic assessments on C1D1, C1D2, and C1D8, subjects should take the drug at the study center under the supervision of study personnel. On C1D2, C1D3, C1D4, and C1D5, LAM-003 is to be administered in the study center and only after the serum chemistry results from that day have been evaluated to exclude TLS. While variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.4 Starting Dose Levels and Dose Escalation

Changes/Rationale: As requested by FDA, the dose levels of LAM-003A after Dose Level 1 were revised to reflect 1.5-fold increases in dose (rather than 1.75-fold increments), resulting in a maximum dose level of <480 mg/day, which was the MTD dose level in the earlier study of LAM-003A in subjects with solid tumors. References to Part 2 (cohort expansion) were removed consistent with the revised study design.

~~In Part 1, c~~Cohorts of 3 to 6 subjects will be 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 will be 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 TEAE requiring dose modifications to levels below Dose Level 1. ~~In Part 2, expansion cohorts will receive the RDR established in Part 1 of the study.~~

Table 1: LAM-003 Starting Dose Levels

Dose Level	LAM-003 Dosing Regimen	Dose Change Relative to Prior Dose
~~Part 1 (Dose Escalation)~~		
-2	50 QD	0.50
-1	100 QD	0.50
1 (initial dose level)	200 QD	Not applicable
2	~~350~~ 300 QD	~~1.75~~1.50
3	~~500~~ 450 QD	~~1.75~~1.50
~~Part 2 (Cohort Expansion)~~		
~~Not applicable~~	~~RDR~~	~~Not applicable~~

Abbreviations: QD=once per day~~, RDR=recommended dosing regimen~~

~~During Part 1 of the study, the~~The following dose-escalation rules will be employed, considering DLTs observed in Cycle 1 of therapy:

- Each dose level cohort will initially enroll 3 subjects.
- If 0 of the first 3 subjects has a DLT, the next cohort of 3 subjects will be treated at the next higher dose level.
- If 1 of the first 3 subjects in a cohort experiences a DLT, an additional 3 subjects will be treated at that same dose level. If 0 of the additional 3 subjects experience a DLT, the next cohort of 3 subjects will be treated at the next higher dose level.
- If ≥2 of 3 or ≥2 of 6 subjects experience a DLT, the MTD will have been exceeded and 3 more subjects will be treated at the next lower dose level (if only 3 subjects were previously treated at that prior dose level). If 6 subjects were previously treated at the prior dose level, that prior dose level will provisionally be considered the MTD.
- An additional 6 subjects (up to 12 total) may be enrolled at the MTD or RDR.
- With the concurrence of the SRC, additional subjects (up to 12 subjects per dose level) may be accrued at dose levels at or below the MTD to refine the estimation of the RDR and further define the pharmacology of LAM-003. Such accrual may occur:
  - At Dose Level -1 or -2 (100 or 50 mg of LAM-003, respectively).
  - At an initially planned dose level (as indicated in Table 1) or at a dose level that lies between the initially planned dose levels.
  - Using an alternative schedule (eg, BID) with a total daily dose that does not exceed the total daily MTD.

The following additional procedures will be followed during the dose escalation:

- The first subject to be treated at Dose Level 1 will be observed for ≥1 week after initiation of LAM-003 before any subsequent subjects are treated at the same dose level.
- Each group of 3 subjects within a cohort must receive ≥75% (21/28 doses for a QD schedule or 42/56 doses for a BID schedule) of planned Cycle 1 LAM-003 doses per subject and must be observed for a minimum period of 4 weeks without DLT before subsequent subjects are enrolled at the next higher dose level. Any subject without DLT who does not complete these requirements may be replaced.
- Escalation to the next dose level ~~or progression to the expansion portion of the study~~ can only occur upon review of the available safety data from all ongoing and previous subjects and with the concurrence of the SRC.
- Intrasubject dose escalation above the initially assigned dose level will be not be permitted except as defined in Section 6.2.7 below.
- Accrual of additional subjects to a treatment cohort may be considered by the SRC with the concurrence of the study sponsor.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.5 Definition of DLTs

Changes/Rationale: As requested by the FDA, hematologic toxicity (Grade 4 neutropenia) was added as a DLT and the DLT criteria for visual disturbances and TLS were revised.

Based on this information but considering the limited experience with LAM-003/LAM-003A, DLTs for the purposes of establishing the MTD and RDR in this study will be defined as any of the following TEAEs occurring in Cycle 1 of LAM-003 therapy that cannot be considered incontrovertibly related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication:

- Grade 4 neutropenia persisting for >28 days
- Grade ≥3 vomiting despite recommended antiemetic support
- Grade ≥3 diarrhea despite recommended antidiarrheal support
- Grade ≥2~~3~~ visual disturbances
- Grade ≥2 heart failure or ventricular dysfunction
- Grade 3 TLS despite adequate prophylaxis (unless TLS results in no Grade >2 renal dysfunction or other Grade >2 end-organ injury and resolves <7 days from onset)
- Grade ≥4 TLS despite adequate prophylaxis
- Other Grade ≥3 nonhematological AEs (with the exception of asymptomatic Grade ≥3 laboratory abnormalities that improve to Grade ≤2 within 72 hours)
- The occurrence of either of the following circumstances during Cycle 1:
    - Inability to comply with ≥75% (21/28 doses for a QD schedule or 42/56 dose for a BID schedule) of planned LAM-003 doses due to an AE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication

- Following a dose interruption starting in Cycle 1, failure to recover to baseline within ~~3~~2 weeks from the last dose of LAM-003 due to a TEAE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication; occurrence of such a TEAE should also result in permanent discontinuation of study drug (see Section 6.5)

~~Hematological findings will not be considered as DLTs given preexisting disease-related myelosuppression in patients with AML and the lack of concerning hematological toxicity observed within the planned dose range based on the prior clinical experience with LAM-003A.~~

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.7 Dose Modification Recommendations

Changes/Rationale: As recommended by FDA, the previous dose modification recommendations for LAM-003 were revised to 1) make dose modifications for toxicities mandatory, 2) ensure that dose reductions are done in accordance with the protocol-specified dose levels, 3) state that subjects who cannot tolerate LAM-003 after 2 progressive dose reductions or a decrease to Dose Level -2 (50 mg/day) should be discontinued from study drug therapy, 4) clarify that subjects whose dose is de-escalated are not eligible for dose re-escalation if they have experienced Grade >2 toxicities at the current dose level, 5) clarify resumption of LAM-003 therapy in subjects who experience AEs that preclude resumption of therapy by Day 29, and 6) provide additional dose-modification guidelines for subjects who experience treatment-emergent visual toxicities.

~~Recommendations for modifications of study drug dosing comprise guidelines; variations from these recommendations may be warranted based on judgments in considering potential risks, benefits, and therapeutic alternatives available to each subject. In addition, investigators should consider and eliminate other potential causes for AEs (eg, underlying malignancy, intercurrent illness, comorbid conditions, or concomitant medications).~~

If a subject experiences an AE that is suspected to be related to the study drug, appropriate monitoring and supportive care (eg, antiemetics, antidiarrheals, therapy for TLS) should be instituted consistent with the nature of the event.

If a subject experiences a Grade 4 toxicity (other than Grade 4 TLS recovering with no adverse sequalae), then the study drug administration should be permanently discontinued. If a subject experiences a DLT or a less severe AE that the investigator believes warrants dose modification, then the study drug administration should be interrupted until the toxicity recovers to Grade ≤1 or baseline. ~~A decision should be made as to whether the subject can reasonably continue with the study drug based upon the nature and severity of the AE.~~ In addition, subjects who develop treatment-emergent dose-limiting visual symptoms should undergo more frequent ophthalmological consultation (eg, at ~2-week intervals or more frequently, as appropriate) (see Section 6.3.13). If the drug is resumed after a dosing interruption, the dose of LAM-003 should be reduced by 1 dose level (reference Table 1)~~ unless a lesser decrement in dose is permitted by the medical monitor.~~ Two successive adjustments to progressively lower dose levels can be made. If the subject cannot tolerate LAM-003 after a decrease in dose by 2 dose levels or to Dose Level -2 (50 mg/day), then the subject should be discontinued from study drug therapy ~~unless continued treatment is permitted by the medical monitor~~.

In general, after the LAM-003 dose is reduced, the dose should be maintained at that dose level, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of LAM-003 for ≥4 weeks with no toxicities of Grade ≥2, then the LAM-003 dosing regimen may be reescalated to the next higher dose level ~~at the discretion of the investigator~~ if the AE that prompted the dose reduction comprised TLS or if further evaluation reveals that the AE that led to the dose reduction was incontrovertibly related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication. Successive adjustments to progressively higher dose levels can be made. However, during the first 2 cycles of therapy, the escalated dose cannot exceed the starting dose level for that subject.

Individual subjects who initiated treatment at a dose level below the lower of the currently established MTD may have the LAM-003 dose escalated to the next higher dose level after ≥2 cycles of therapy if both the principal investigator and the medical monitor agree that the subject is tolerating the current dose level with no toxicities of Grade ≥2 and that a dose escalation is medically warranted (~~e~~gie, for a subject with a ~~partial remission~~PR). In such subjects, successive adjustments to progressively higher dose levels can be made at intervals of ≥4 weeks with the caveat that the escalated dose level cannot exceed the currently established MTD.

~~In a subject who experiences a DLT precluding resumption of LAM-003 therapy during a cycle, a new cycle of treatment may begin at the later of Day 29 of the current cycle or when AEs or laboratory abnormalities have returned to baseline levels. If AEs or laboratory abnormalities preventing further administration of study drug are not resolved to baseline by Day 29 of the current cycle, week-by-week delays in initiating the new cycle of treatment should be instituted. When AEs and laboratory abnormalities have returned to baseline, the next cycle of therapy can be initiated. Upon initiation of a new cycle, the prior cycle of therapy will be considered completed.~~ In a subject who experiences an AE precluding resumption of LAM-003 therapy by Day 29 of the current cycle (planned Day 1 of the next cycle), the new cycle of treatment may only begin when AEs or laboratory abnormalities have returned to baseline levels and if the subject does not meet criteria for permanent discontinuation of study therapy (see Section 6.5). Upon initiation of a new cycle, the current cycle will be considered completed.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.3 Supportive Care, 6.3.11 Hematopoietic Support

Changes/Rationale: As requested by the FDA , the use of hematopoietic agents as supportive care was revised to conform to NCCN guidelines.

LAM-003 is not expected to cause myelosuppression based on nonclinical and clinical experience with LAM-003A. However, subjects may experience hematological AEs related to the underlying AML or prior therapy.

Granulocyte colony-stimulating factor (G-CSF) (eg, filgrastim, filgrastim-snd, peg-filgrastim, lenograstim) or granulocyte-macrophage colony-stimulating factor (GM-CSF) (eg, sargramostim) may be administered in response to neutropenic complications, as appropriate and consistent with current guidelines [NCCN 2017a, NCCN 2017c].

~~GM-CSF should not be administered given the potential for GM-CSF-related inflammatory symptoms.~~

Use of erythropoietic agents (eg, erythropoietin or darbepoetin) is not recommended based on current guidelines [NCCN 2017b].

Red blood cell or platelet transfusions may be administered as medically indicated.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.3 Supportive Care, 6.3.13 Ophthalmological Symptom Management

Changes/Rationale: As requested by the FDA, the section was revised to provide additional guidance on ophthalmologic follow-up for subjects who experience dose-limiting visual toxicities and to clarify resumption of LAM-003 therapy in such subjects.

During the study, subjects will undergo screening and periodic ophthalmological examinations (eg, visual acuity testing, ~~with~~ electroretinography, and slit lamp examination ~~and dark adaptometry~~) according to the schedule of activities provided in Section 7. As noted in Section 6.2.7 ~~In addition,~~ subjects who develop treatment-emergent dose-limiting visual symptoms should have drug interrupted and should undergo more frequent ophthalmological consultation (eg, at ~2-week intervals or more frequently, as appropriate). Symptoms should resolve to Grade ≤1 before resumption of study drug and study drug should only be resumed if such resolution occurs within 2 weeks of interruption of study drug and the subject appears to be otherwise safely benefiting from study therapy.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.3 Supportive Care, 6.3.14 TLS Management

Changes/Rationale: As requested by the FDA, additional guidance for monitoring of TLS was included.

Subjects must be monitored for TLS during on C1D1 through C1D5 with assessment of vital signs, AEs, and serum chemistry and hematology laboratory studies as described in Section 7. Subjects who develop TLS may experience hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, acute renal failure, and cardiac dysrhythmias ~~, and acute renal failure~~; thus, close monitoring of electrolytes, serum creatinine, and vital signs is particularly important after initial therapy. ECG monitoring should also be instituted in subjects with biochemical abnormalities suggestive of TLS.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.5 Duration of Study Drug Administration and Study Participation

Changes/Rationale: The reasons for treatment discontinuation were clarified and expanded based on FDA recommendations.

Subjects may receive LAM-003 therapy indefinitely. However, the occurrence of any of the following events requires treatment discontinuation:

- Subject request to withdraw from study treatment
- Documented objective evidence of treatment failure or of AML relapse or progression (see Section 10.4.5 and Section 10.4.6 for definitions) while receiving study treatment
- For a subject in PR, continued red blood cell transfusion dependence at Week 20
- Intolerable toxicity despite appropriate supportive care and/or dose modification

- Failure to recover to Grade ≤1 or baseline within 2 weeks from the last dose of LAM-003 following interruption for a TEAE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication
- The development of intercurrent illness or other substantial change in the subject's condition or circumstances that would place the subject at unacceptable risk as determined by the study investigator in consultation with the medical monitor
- Initiation of treatment for the subject's cancer with an off-study therapeutic regimen
- Pregnancy or breastfeeding
- Substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results
- Discontinuation of the study by the study center, the sponsor, relevant regulatory agencies, or the IRB/IEC

Unless they withdraw consent for further follow-up, subjects who discontinue study therapy will continue on study for acquisition of safety information through ≥30 days after the last dose of study treatment, and for further collection of information regarding additional therapies for their cancer and OS.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.6 Rationale for Study Drug Administration and Supportive Care

Changes/Rationale: Additional rationale was provided for QD and BID dosing regimens based on a comment from FDA.

Both one-per-day (QD) and twice-per-day (BID) dosing were explored in the Phase 1 study of LAM-003A in patients with solid tumors. It appeared that the total daily dose of LAM-003A was most important in defining the safety profile; the study did not suggest a schedule-dependent safety concern with either the QD or BID dosing regimen. Further, the average half-life (t1/2) after repeated dosing of LAM-003A was 11.2 hours, supporting use of either QD or BID dosing. Based on these observations, the current study will initially evaluate LAM-003 using a QD dosing regimen because such dosing could potentially minimize the likelihood of TLS (by avoiding administration of a C1D1 evening dose in the face of potential TLS-mediated renal dysfunction). In addition, food-effect data are not yet available; thus, QD dosing in the morning is appropriate to increase the likelihood that the drug will consistently be administered in a fasting state. Further, QD dosing offers convenience advantages for patients. BID dosing may be explored in this protocol once there is more safety, pharmacokinetics, and pharmacodynamic experience with the drug using the initial QD regimen.

Changes to: Section 7 STUDY ACTIVITIES AND ASSESSMENTS

Changes/Rationale: The schedule of activities (Table 3) was updated to reflect additional TLS monitoring. Visit windows after C1D8 were expanded per site request.

Table 3: Schedule of Activities

	Screening	Therapy											Posttherapy Follow-up	
		Cycle 1							Cycle 2		Cycle ≥3	End of Therapy Visit		
Day	**-28 to -1 [a]**	**1 [b]**	**2**	**3**	**4**	**5**	**8**	**15**	**1**	**15**	**1**		**≤30 days**	**Long-term**
Visit Window, days							**±2**	**±2~~3~~**	**±2~~3~~**	**±2~~3~~**	**±2~~3~~**	**+14**		
General Eligibility/Safety Assessments														
Written informed consent [c]	X													
Medical history [d]	X													
Height [e]	X													
Weight [f]	X	X	X	**X**	**X**	**X**	X		X		X	X		
Vital signs/oxygen saturation [g]	X	X	X	**X**	**X**	**X**	X		X		X	X		
Performance status [h]	X	X					X		X		X	X		
AE assessment [i]	X	X	X	**X**	**X**	**X**	X	X [i]	X	X [i]	X	X	X	
Concomitant medications [j]	X	X	X	**X**	**X**	**X**	X	X [j]	X	X [j]	X	X	X	
12-lead ECG [k]	X	X	X				X		X			X		
Ophthalmological examination [l]	X								X [l]		X [l]	X		
Study Drug Administration/Dispensing/Return														
TLS prophylaxis as needed [m]	X	X												
LAM-003 administration in clinic [n]		X	X	**X**	**X**	**X**	X							
Dispensing of LAM-003 [o]			~~X~~			**X**			X		X			
LAM-003 return/compliance check [p]									X		X	X		
Laboratory Assessments														
Urinalysis [q]	X	X	X						X			X		
Serum virology [r]	X													
Serum pregnancy test [s]	X	X							X		X	X		
Serum chemistry [t]	X	X	X	X	X	X	X	X [t]	X	X [t]	X	X		
Hematology [u]	X	X	X	X	X	X	X	X [u]	X	X [u]	X	X		
Coagulation [v]	X	X	X						X			X		
Plasma for LAM-003 pharmacokinetics [w]		X	X				X							
Blood for AML FLT3-ITD/HSP protein expression [x]		X	X				X		X					
Blood for AML HSP gene expression [y]		X	X				X		X					
Plasma for FL concentrations [z]		X	X				X		X					
Blood for AML PD-L1 expression [aa]		X	X				X		X					
Blood for immune cell profiling [bb]		X					X		X					
Disease-Related Assessments														
Blood for FLT3-ITD mutation [dd]	X													
Blood/saliva for AML/control mutation profiling [ee]		X												
Blood and bone marrow aspiration/biopsy [ff]	X										X [ff]	X [ff]		
Radiology examination [gg]	X										X [gg]	X [gg]		
Posttherapy Follow-up														
Posttherapy safety assessment [hh]													X	
Long-term follow-up [ii]														X

Footnotes	
N*ote:*	***For scheduled visits after C1D1, permitted visit windows are indicated in the table. For procedures to be performed at a specified time postdose, the acceptable margin for actual time is as follows for hours (±minutes): 0.5 (±5), 1 (±15), 2 (±15), 4 (±15), 6 (±15), 8 (±15), 24 (±60). If multiple procedures are to be done at the same timepoint, the preferred order is vital signs, blood sampling, and then ECG, with blood sampling occurring as close as possible to the specified time.***
a.	To optimize scheduling convenience for the subject and for the study center staff, Screening procedures may be performed over as many days as necessary provided that screening activities (excepting prestudy tumor evaluation) are completed within 28 days before C1D1 of the study.
b.	If obtained within 3 days prior to the start of therapy, urinalysis and serum pregnancy, serum chemistry, hematology, and coagulation studies collected during Screening need not be repeated on C1D1.
c.	Written informed consent will be obtained before performance of any study procedures that are not part of routine medical care.
d.	Medical history to include recording of cancer history, previous therapy for cancer, past and ongoing medical conditions, review of systems, and relevant social history.
e.	Height (in centimeters) will be obtained at Screening only.
f.	Weight (in kilograms) will be obtained once on each designated day.
g.	Vital signs (blood pressure, pulse, temperature, and oxygen saturation via pulse oximetry) will be obtained with the subject resting in a supine position while breathing room air. Vital signs will be 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), C2D1, C≥3D1, and at End of Therapy.
h.	Performance status will be assessed using ECOG scale (see Appendix 14.114.1) once on each designated day.
i.	AEs will be described using concise medical terminology, including whether serious, the date of onset, the date of resolution, severity based on the CTCAE (Version 4.03) [NCI 2010], a description of potential relatedness to the study drug or to a study procedure, the action taken due, and the outcome. On C1D15 and C2D15, AE information may be obtained via telephone contact with the subject.
j.	Concomitant medication assessments should include information regarding all prescription, nonprescription, illicit, and alternative medications (health foods). Use of any supportive care (eg, antidiarrheals, antiemetics, hematopoietic growth factors, transfusions) should be noted. On C1D15 and C2D15, concomitant medication information may be obtained via telephone contact with the subject.
k.	12-lead ECGs will be obtained with the subject resting in a supine position. ECGs will be collected at Screening, C1D1 (predose [in triplicate], 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.
l.	Ophthalmologic evaluations (eg, with visual acuity testing, electroretinography, slit lamp examination ~~dark adaptometry~~) should be performed by an ophthalmologist during Screening, within 14 days before C2D1, within 14 days before C4D1 (8-week interval), and then within 14 days before C7D1, C10D1, C13D1, C16D1, etc (12-week intervals), and at End-of-Therapy.
m.	If TLS is observed during study conduct, subjects who are at intermediate or high risk of TLS should receive medical prophylaxis according to the protocol-recommended or an institutional regimen customarily used at the study center (see Section 6.2.1.2).
n.	The dose of LAM-003 will be administered to the subject in the study center (with recording of the date and actual clock time of the LAM-003 administration). On C1D2, C1D3, C1D4, and C1D5, LAM-003 should only be administered after the serum chemistry results from that day have been evaluated to exclude TLS.
o.	Study centers will ensure that subjects have a sufficient supply of LAM-003 and are provided with instructions for self-administration at home.
p.	Empty, partially used, or full bottles of LAM-003 will be retrieved from the subject and drug compliance will be assessed.
q.	Urinalysis to include specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick and white blood cells, red blood cells, epithelial cells, bacteria, cast and crystals as assessed by microscopy. Urinalysis should be performed once on each designated day.
r.	Virology evaluation to include serum HIV antibody, HbsAg antibody, HBc antibody, HCV antibody. Subjects with a positive antibody evaluation for HBc or HCV should undergo evaluation for HBV DNA and for HCV RNA to determine if the antibody test may be falsely positive.
s.	Serum pregnancy testing will be performed in women of childbearing potential only. Pregnancy testing should be performed once on each designated day.
t.	Serum chemistry studies to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, ALP, CK, LDH, total bilirubin, uric acid. Serum chemistry studies should be performed once on each designated day. On C1D2, C1D3, C1D4, C1D5, serum chemistry results from that day should be evaluated to exclude TLS before the subject is administered LAM-003 in the clinic. On C1D15 and C2D15, serum chemistry studies may be obtained at a local laboratory.
u.	Hematology to include hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils; platelet

	count. Hematology testing should be performed once on each designated day. On C1D15 and C2D15, hematology studies may be obtained at a local laboratory.
v.	Coagulation studies to include PT and aPPT. Coagulation studies should be performed once on each designated day.
w.	Plasma for LAM-003 pharmacokinetics will be collected on C1D1 (predose, and at 0.5, 1, 2, 4, 6, and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), and on C1D8 (predose, and at 0.5, 1, 2, 4, 6, and 8 hours postdose).
x.	Blood for FLT3-ITD/HSP protein expression in AML blasts will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.
y.	Blood for HSP gene expression will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.
z.	Plasma for FLT3 ligand concentrations will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.
aa.	Blood for AML PD-L1 expression will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.
bb.	Blood for immune cell profiling will be collected on C1D1 (predose), C1D8 (predose), and C2D1.
cc.	Blood for FLT3-ITD mutation confirmation in AML blasts using the LeukoStrat® CDx FLT3 mutation assay will be obtained during Screening.
dd.	Blood for AML cell mutation profiling with collection of saliva as a germline DNA control will be obtained on C1D1 (predose).
ee.	Blood for peripheral blood AML blast count evaluation and bone marrow aspiration/biopsy will be performed during Screening (unless the requirement for screening bone marrow aspirate/biopsy is waived by the medical monitor because sufficient bone marrow material is available for response determination). Post-baseline, a bone marrow aspirate/biopsy is required within 14 days before C3D1, C5D1, C7D1 (8-week intervals), and then within 14 days before C10D1, C13D1, C16D1, etc (12-week intervals). An End-of-Therapy bone marrow aspirate/biopsy should be performed unless the subject already has hematological or radiographic confirmation of DRP ≤8 weeks before permanent study drug discontinuation. At all AML evaluations, the extent of involvement with AML in peripheral blood and bone marrow, the presence of Auer rods, and bone marrow cellularity will be assessed. Bone aspirate aliquots obtained at Screening and within 14 days before C3D1 may also be evaluated for FLT3-ITD, HSP protein and gene expression, PD-L1, and AML mutations.
ff.	Radiology examination is required in subjects with extramedullary disease that is radiographically assessable. FDG-PET/CT is the preferred method of evaluation but other methods (diagnostic CT, MRI) may be used if appropriate for the type of lesion. The baseline evaluation should occur within 28 days before C1D1. Post-baseline evaluations should be performed within 7 days before C3D1, C5D1, C7D1 (8-week intervals), and then within 7 days before C10D1, C13D1, C16D1, etc (12-week intervals). An End-of-Therapy radiology assessment should be performed unless a subject with extramedullary disease already has hematological or radiographic confirmation of DRP ≤8 weeks before permanent study drug discontinuation.

gg.	Posttherapy safety assessment will be performed after permanent cessation of study therapy to follow subjects for any drug-related AE and/or ongoing SAEs. Subjects will be followed until the later of either 30 days after the last dose of study treatment or until resolution/stabilization of any ongoing drug-related AEs and/or SAEs. Follow-up may be obtained in person or by telephone contact.
hh.	Long-term follow-up information will be obtained in all surviving subjects who permanently discontinue study therapy. Data on post-study therapies for the AML and on survival will be collected. Such information may be collected at ~3- to 6-month intervals through 3 years. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

Abbreviations: AE=adverse event, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AML=acute myeloid leukemia, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CK=creatine kinase, CT=computed tomography, CTCAE=Common Terminology Criteria for Adverse Events, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, FDG=fluorodeoxyglucose, FL=FLT3 ligand concentration, FLT3= FMS-like tyrosine kinase-3, HBc antibody=hepatitis B core antibody, HbsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HSP=heat shock protein, ITD=internal tandem duplications, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, NK=natural killer (cells), PD-L1=programmed death-ligand 1, PET=positron emission tomography, PT=partial thromboplastin time, RNA=ribonucleic acid, SAE=serious adverse event, TLS=tumor lysis syndrome

Changes to: Section 8 SAFETY ASSESSMENTS, 8.7 Study Center Reporting Requirements, 8.7.3 Contact Information for Report and SAE or Pregnancy

Changes/Rationale: The facsimile number of the pharmacovigilance group was added.

Contact information for reporting an SAE or pregnancy is provided in Table 7.

Table 7: Contact Information for Reporting SAEs or Pregnancies

Pharmacovigilance CRO	Contact Information
Pharmalex US, LLC, Guilford, CT, USA	E-mail: Vigicare@pharmalex.com
	Facsimile: +1 (617) 315-4825

CRO=contract research organization, SAE=serious adverse event

Changes to: Section 9 LABORATORY AND OTHER ASSESSMENTS, 9.1 Methods and Analytes

Changes/Rationale: Text in the body of this section and in Table 8 was updated to describe the ophthalmological examinations and the appropriate testing equipment. The disease-related laboratory parameters in Table 8 were revised to include an assessment of minimal residual disease.

Ophthalmological examinations should be performed by a consulting ophthalmologist or optometrist with the necessary facilities and equipment to perform appropriate testing (eg, visual acuity testing, electroretinography, slit lamp examination ~~dark adaptometry~~); interpretations of ophthalmological findings will be provided by a consulting ophthalmologist).

Table 8: Laboratory and Other Parameters to Be Assessed

Laboratory – Disease-related	
Peripheral blood or bone marrow cellular AML FLT3-ITD mutation analysis	• Peripheral blood or bone marrow AML blast FLT3 mutation type and FLT3 ITD mutation-to-WT allele ratio (as evaluated using the LeukoStrat® CDx FLT3 mutation assay)
Baseline biomarker assessment	• Mutational profiling in DNA from peripheral blood AML blasts with saliva as germ-line DNA control (with sample analysis using NGS)
Peripheral blood smears and bone marrow aspirate and biopsy for efficacy assessments	• Peripheral blood smears and bone marrow aspirate and biopsy for analysis of AML disease status (blast percentage, presence of Auer rods, bone marrow cellularity, MRD) (as assessed by Wright stain for peripheral blood and bone marrow aspirate, hematoxylin and eosin for bone marrow biopsy, flow cytometry, and immunohistochemistry ~~or flow cytometry~~ [as needed for ambiguous blast analysis])
Other	
Body weight/height	• Weight in kilograms, height in centimeters
Body temperature	• Temperature in degrees Celsius
Blood pressure	• Diastolic and systolic blood pressure in mm Hg
Oxygen saturation	• % saturation
Ophthalmology examination	• Examination by an ophthalmologist (~~to include~~eg, visual acuity testing, electroretinography, slit lamp examination ~~and dark adaptometry, if appropriate~~)
12-lead ECG	• Heart rate, cardiac intervals, wave form abnormalities, ectopy
Radiology examination	• FDG-PET/CT (preferred), MRI, or diagnostic CT imaging for subjects with extramedullary disease that is radiographically assessible.

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AML=acute myeloid leukemia, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CD=cluster of differentiation, CK=creatine kinase, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, FDG=fluorodeoxyglucose, FL=FLT3 ligand, FLT3= FMS-like tyrosine kinase-3, HBc antibody=anti-hepatitis B core antibody, HbsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HSP=heat shock protein, IFNγ=interferon-γ, LDH=lactate dehydrogenase, MRD=minimal residual disease, ITD=internal tandem repeat, MRI=magnetic resonance imaging, NGS=next-generation sequencing, NK=natural killer (cells), PET=positron emission tomography, PCR=polymerase chain reaction, PD-L1=programmed death (receptor) ligand-1, PT=prothrombin time, RNA=ribonucleic acid, WT=wild type, β-HCG=β-human chorionic gonadotropin.

Changes to: Section 10 EFFICACY ASSESSMENTS, 10.4, Definitions of Tumor Remission and Progression

Changes/Rationale: The criteria for CR_{MRD} were added, references to RBC transfusions as a component of response were removed from the definitions of complete remission with incomplete blood count recover (CRi) and partial remission (PR) for consistency with 2017 ELN proposals for response criteria), and the criteria for disease relapse or progression for MRD were added.

10.4 Definitions of Tumor Remission and Progression

Responses will be categorized as complete remission without minimal residual disease (CR_{MRD}), complete remission (CR), complete remission with incomplete blood count recovery (CRi), partial remission (PR), disease recurrence or progression (DRP), or treatment failure (TF). In

addition, a remission category of nonevaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize remission status.

The best overall response will be determined. The best overall response is the best on-treatment response from baseline recorded from the start of treatment until DRP or TF. The baseline status will be taken as a reference for determinations of response. The best on-study measurement will be taken as a reference for DRP; the best on-study measurement constitutes the measurement with the least tumor involvement, including the baseline measurement if this is the measurement meeting this criterion.

10.4.1 Complete Remission without Minimal Residual Disease

To satisfy criteria for CR_{MRD}, all of the following conditions must be attained:

- Leukemia disease status meeting all of the following requirements:
  - Absence of evidence of AML in bone marrow aspirate by flow cytometry
  - ≤5% bone marrow blasts (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - No blasts in the peripheral blood
  - No blasts with Auer rods
  - No extramedullary disease
- Peripheral blood meeting both of the following requirements:
  - ANC >1.0 × 10^9/L
  - Platelet count >100 × 10^9/L

10.4.2 Complete Remission

To satisfy criteria for CR, all of the following conditions must be attained:

- Leukemia disease status meeting all of the following requirements:
  - <5% bone marrow blasts (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - No blasts in the peripheral blood
  - No blasts with Auer rods
  - No extramedullary disease
- Peripheral blood meeting ~~all~~ both of the following requirements:
  - ANC ≥1.0 × 10^9/L
  - Platelet count ≥100 × 10^9/L
  - ~~No requirement for red blood cell transfusions to maintain hemoglobin~~

10.4.3 Complete Remission with Incomplete Blood Count Recovery

To satisfy criteria for CRi, all of the following conditions must be attained:

- Leukemia disease status meeting all of the following requirements:
  - <5% bone marrow blasts (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - No blasts in the peripheral blood
  - No blasts with Auer rods
  - No extramedullary disease
- Peripheral blood meeting ~~any~~ either of the following requirements:
  - ANC <1.0 x 10^9/L
  - Platelet count <100 x 10^9/L
  - ~~Requirement for red blood cell transfusions to maintain hemoglobin~~

10.4.4 Partial Remission

To satisfy criteria for PR, all of the following conditions must be attained:

- Leukemia disease status meeting either of the following requirements:
  - A ≥50% decrease in bone marrow blasts to 5% to 25% (inclusive) (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - <5% bone marrow blasts but with Auer rods present (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules)
  - No blasts in the peripheral blood
  - No new or worsening extramedullary disease
- Peripheral blood meeting ~~all~~ both of the following requirements:
  - ANC ≥1.0 × 10^9/L
  - Platelet count ≥100 × 10^9/L
  - ~~No requirement for red blood cell transfusions to maintain hemoglobin~~

10.4.5 Treatment Failure

The occurrence of any of the following events indicates TF:

- In a subject without DRP, inability to qualify for a CR_{MRD}. CR, CRi, or PR by ~~56 days~~ 8 weeks from start of study therapy
- In a subject without a CR_{MRD}. CR, CRi, PR, or DRP, permanent cessation of study therapy due to an AE
- In a subject without a CR_{MRD}. CR, CRi, PR, or DRP, death from any cause

10.4.6 Disease Relapse or Progression

The occurrence of any of the following events indicates DRP:

- Reappearance of bone marrow blasts to >5% in a subject who had experienced a CR or CRi
- Reappearance of blasts in the peripheral blood in a subject who had experienced a CR, CRi, or PR
- An absolute 20% increase in bone marrow blasts to >25% (based on a bone marrow aspirate/biopsy sample with ≥200 nucleated cells and the presence of bone marrow spicules) in a subject who had experienced a PR
- Development of new or worsening existing extramedullary disease
- Recurrence or worsening of MRD, as assessed by flow cytometry, will not be considered in the definition of DRP, but will be recorded.

10.4.7 Nonevaluable

In a subject who does not have TF or DRP, the occurrence of any of the following conditions indicates a remission status of NE:

- Bone marrow aspiration/biopsy data are inadequate or missing
- Peripheral blood data are inadequate or missing
- Information for a known site of extramedullary disease is inadequate or missing

Changes to: Section 11 STATISTICAL CONSIDERATIONS, 11.1 Analysis Conventions, 11.1.1 Analysis Sets

Changes/Rationale: The definitions of the full analysis set and responding analysis set were modified to include CR_{MRD} as a response category.

11.1.1 Analysis Sets

11.1.1.1 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.

11.1.1.2 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

Changes to: Section 11 STATISTICAL CONSIDERATIONS, 11.1.2 Data Handling Conventions, and 11.2.1 Subject Disposition and Baseline Characteristics

Changes/Rationale: The text was revised to reflect the change in study design (removal of Part 2 of the study).

11.1.2 Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Data will be described and summarized by dosing regimen ~~study part (Part 1 or 2), dose level (Part 1),~~ and time point.

11.2.1 Subject Disposition and Baseline Characteristics

A listing of all full analysis subjects will be generated to describe study center, subject number, first screening date, first treatment date, ~~study part (Part 1 or 2), dose level (Part 1)~~ dosing regimen, the longest duration of treatment with LAM-003, and the reason for discontinuing LAM-003. Available information on subjects who were screened but not administered study drug may be listed separately. A table will be created summarizing these categories in terms of number and percent for the full analysis set.

Changes to: Section 11 STATISTICAL CONSIDERATIONS, 11.2 Analysis Plan, 11.2.6 Efficacy Analyses and 11.2.6.1 Categorical Endpoints

Changes/Rationale: The text was revised to reflect the addition of the CR_{MRD} response category.

11.2.6 Efficacy Analyses

Tumor control will be documented at each assessment by remission category (eg, CR_{MRD}, CR, CRi, PR, TF, DRP, or NE, as defined for each response parameter (see Section 10.4), date that response is first documented, and date of tumor progression/failure. MRD status, as assessed by flow cytometry, will be recorded.

11.2.6.1 Categorical Endpoints

OR, CRc, CR_{MRD},CR, CRi, and PR rates will be described. In analyses of response rates in the full analysis set, subjects who have best responses of TF, DRP, or NE will be counted as failures. For all analyses of response rates, the relevant Cis will be presented.

Changes to: Section 11 STATISTICAL CONSIDERATIONS, 11.3 Timing of Analyses, 11.3.1 Interim Analyses and 11.3.2 Final Analyses

Changes/Rationale: The sections were revised to remove references to Part 2 (cohort expansion) consistent with the revised study design.

11.3.1 Interim Analyses

~~In Part 1 of the study,~~N ~~n~~o formal interim analyses are planned. As described in Section 2.2, conference calls among the members of the SRC will be conducted periodically to discuss study progress, exchange study information, and 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, LAM may collate and summarize available study results during conduct of the study.

~~In Part 2 of the study, a rate of discontinuations of therapy due to AEs of ≥20% would suggest excessive toxicity due to study therapy. Sequential Pocock-type boundaries will be used to continuously monitor the rate of AE discontinuations and to test the null hypothesis, after each subject (to the maximum potential sample of 18 subjects), that the event rate is ≥0.20 using a 1-sided significance test of <0.05. AE discontinuation rates will be considered excessive if the following n/N values are observed: -/1, -/2, 3/3, 4/4, 4/5, 4/6, 5/7, 5/8, 5/9, 6/10, 6/11, 6/12, 7/13, 7/14, 7/15, 8/16, 8/17, 8/18. With this method, the probability of detecting an AE discontinuation safety signal ranges from 0.048 to >0.810 for true AE discontinuation rates of 20% to ≥50%. If excessive levels of AE discontinuation are observed, the study sponsor, working in collaboration with the investigators, will take appropriate actions (eg, continuation with modifications in design, dosing regimen, and/or monitoring plan; interruption of expansion cohort accrual; discontinuation of expansion cohort therapy).~~

11.3.2 Final Analyses

~~As appropriate, Part 1 may be reported separately from Part 2 of the study.~~ Final study reporting ~~for Part 1~~ is expected to occur after all ~~Part 1~~ subjects have discontinued study treatment or ≥48 weeks after accrual of the final subject (whichever occurs earlier). ~~Final study reporting for Part 2 is expected to occur after all subjects have discontinued study treatment or ≥48 weeks after accrual of the final subject (whichever occurs earlier).~~

Section 11 STATISTICAL CONSIDERATIONS, 11.4 Basis for the Planned Sample Sizes

Changes/Rationale: The sections were revised to remove references to Part 2 (cohort expansion) consistent with the revised study design.

~~**11.4.1 Part 1 (Dose Escalation)**~~

Sample sizes ~~for Part 1~~ of the cohorts of the study are not based on a specific statistical hypothesis but on experience from similar types of Phase 1 dose-ranging studies in patients with cancer.

In the dose escalation, the cohort sizes of 3 to 6 subjects allow evaluation of regimen safety using a standard definition of MTD (ie, a starting dose associated with DLT in <17% of subjects during the first cycle of therapy). Based on the planned 3+3 dose-escalation scheme, Table 9 shows the probability of escalating to the next dose level or proceeding to the next cohort, based on the true rate of DLT at the current dose level.

Table 9: 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.

~~**11.4.2 Part 2 (Cohort Expansion)**~~

~~Enrollment of 12 evaluable subjects offers the opportunity to determine if there is antitumor activity sufficient to warrant further development of LAM-003 for FLT3-ITD AML. A CRc rate of ≥20% is considered the minimum value of potential interest. If 0/12 evaluable subjects experience a CRc, then a population CRc rate of ≥20% can be excluded with >90% certainty (1-sided exact binomial 90% CI upper bound=17.5%).~~

Changes to: Section 13 BIBLIOGRAPHY

Changes/Rationale: The following modifications or additions were made to the bibliography to support the revisions that were made in this amendment:

NCCN (National Comprehensive Cancer Network). NCCN clinical practice guidelines in oncology: cancer- and chemotherapy-induced anemia. Version 1.2018. 2017b Jun 23. Available at: https://www.nccn.org/professionals/physician_gls/pdf/anemia.pdf (accessed 2017 Nov 10).

NCCN (National Comprehensive Cancer Network). NCCN clinical practice guidelines in oncology: myeloid growth factors. Version 2.2017. 2017c Oct 13. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf (accessed 2017 Nov 10).

14.7 Summary of Changes to Protocol – Amended Version 3

14.7.1 Overview of Changes

The modifications from Version 2 to Version 3 of the protocol included the following:

- Information and implications were included in the protocol regarding additional in vitro drug-drug interaction studies performed with LAM-003A.
- Enrollment procedures were clarified.
- At the request of the investigators, a clarification was included to indicate the extent of TLS that would result in interruption of study drug administration.
- Information regarding severity grading of AEs was corrected.

14.7.2 Specific Changes

In preparing Amended Version 3 of the protocol document, the following specific changes were made. Explanations of the changes are provided in italics as "***Changes/Rationale***". Inserted text is indicated by double-underlining. Deleted text is indicated by ~~strikeout~~. Revisions to the synopsis are not described. Changes to protocol versions and dates, modifications to the list of abbreviations and definitions of terms, routine bibliographic reference updates, or minor typographical or syntax corrections are not indicated.

Changes to: 1 Introduction, 1.4, LAM-003/LAM-003A, 1.4.3 Nonclinical Experience, 1.4.3.3 Pharmacokinetics, Metabolism, and Drug-Drug Interactions

Changes/Rationale: Additional in vitro drug-drug interaction studies were performed with LAM-003A; accordingly, information was included in the protocol regarding the results of these studies and their implications.

(No change to Paragraphs 1-5)

When metabolism was evaluated in human liver microsomes, 7 unique chromatographic peaks were detected by mass spectrometric-detection and the identities of 4 of these peaks were established. ~~The data suggested that LAM-003A is a substrate of cytochrome P450 (CYP) 3A4.~~ All metabolites detected in human microsomes were also detected in rat and/or monkey microsomes. These data confirmed that there were no unique human metabolites relative to toxicology species and that rat and monkey were appropriate species for nonclinical toxicology assessments of LAM-003A.

When evaluated in rats, the primary route of elimination for LAM-003A and metabolites appeared to be through biliary elimination. Renal elimination was negligible (<1%) in rat, dog, and monkey.

To assess for the possibility that LAM-003A metabolism might be altered by other drugs, an in vitro characterization with recombinant cytochrome P450 (CYP) enzymes was performed. This study concluded that LAM-003A was a substrate for the CYP3A4 and CYP3A5 isoforms. Until clinical drug-drug interaction data are available, these nonclinical findings suggest that coadministration of LAM-003 with strong inhibitors or inducers of CYP3A4/5 might perturb LAM-003A exposure and should be minimized (see Section 6.3.9).

The potential for LAM-003 acting as to perpetrate a drug-drug interaction was evaluated in vitro using recombinant CYP enzymes. LAM-003A did not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at concentrations that are likely to be achieved clinically. Inhibition of CYP3A4 was observed with an IC_{50} value of 0.7 μM, suggesting the possibility that LAM-003 could increase systemic exposures to drugs that are sensitive substrates of this enzyme. In a further study in pooled human liver microsomes, LAM-003A did not show direct inhibitory effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. LAM-003A did not show time-dependent inhibition potential against CYP1A2, CYP2B6, CYP2C8, CYP2C19, or CYP2D6. However, LAM-003A demonstrated some evidence of time-dependent inhibition against CYP2C9 with an IC_{50} value of 21.3 μM and more substantial time-dependent inhibition against CYP3A4/5 with IC_{50} values of 0.636 μM (midazolam probe substrate) and 0.499 μM (testosterone probe substrate). Because the prior LAM-003A Phase 1 clinical experience did not demonstrate time-dependent changes in LAM-003A C_{max} and AUC

following repeated dosing, the potential for clinically significant effects of LAM-003 on drugs that are metabolized by CYP3A4 appears to be low. However, investigators are advised to use caution when administering drugs that are sensitive or low-therapeutic-index CYP3A4 substrates (see Section 6.3.9).

Changes to: 5 Recruitment and Selection of Study Subjects, 5.4 Enrollment and Replacement of Study Subjects

Changes/Rationale: Clarifications were included regarding the enrollment procedures.

Inclusion and exclusion criteria will be reviewed for each potential subject by qualified study center personnel. If the consented study candidate is considered eligible for study participation, the study center will transmit a study-specific ~~elegibility~~ eligibility and enrollment form to LAM (or designee).

LAM (or designee) will acknowledge receipt of the study candidate's eligibility form and will complete ~~an~~ the enrollment form indicating the ~~subject identification number, the study part, and the~~ LAM-003 dosing regimen. The enrollment form will be transmitted to the study center. Once the study center receives the completed enrollment form, the subject can begin treatment.

Changes to: 6 Study Drug Information, Administration, and Support, 6.2. Study Drug Administration, 6.2.2. LAM-003 Administration,

Changes/Rationale: A clarification was included to indicate the extent of TLS that should be evaluated to determine the need for interruption of study drug administration. The wording of the change ensured consistency with the TLS DLT definition in Section 6.2.6 that had been previously required by the FDA.

In each 28-day cycle, subjects are to self-administer LAM-003 starting on Day 1 and then continuously thereafter (28 total doses/cycle). Subjects should take the study drug at approximately the same time each day, ideally at ~24-hour intervals (eg, ~8AM every day) for the planned QD schedule or at 12-hour intervals (eg, ~8AM and ~8PM every day) if a BID schedule is evaluated. In conjunction with frequent pharmacokinetic assessments on C1D1, C1D2, and C1D8, subjects should take the drug at the study center under the supervision of study personnel. On C1D2, C1D3, C1D4, and C1D5, LAM-003 is to be administered in the study center and only after the serum chemistry results from that day have been evaluated to exclude Grade 4 TLS or Grade 3 TLS associated with Grade ≥2 renal dysfunction or other Grade ≥2 end-organ injury ~~TLS~~. While variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

Changes to: 6 Study Drug Information, Administration, and Support, 6.3 Supportive Care, 6.3.14 TLS Management.

Changes/Rationale: A clarification was included to indicate the extent of TLS that would result in interruption of study drug administration. The wording of the change ensured consistency with the TLS DLT definition in Section 6.2.6 that had been previously required by the FDA.

(No change to Paragraphs 1 or 2)

Subjects with TLS should receive IV hydration, rapid reversal of hyperkalemia, antihyperuricemic agents, and appropriate cardiac and renal support, including dialysis as indicated. LAM-003 administration may continue except in those who develop Grade 4 TLS or Grade 3 TLS associated with Grade >2 renal dysfunction or other Grade >2 end-organ injury. Upon recovery to baseline functioning and as medically appropriate, ~~such~~ subjects who develop TLS should continue with protocol therapy to maintain tumor control.

Changes to: 7 Study Activities and Assessments

Changes/Rationale: To match other instructions in the protocol related to TLS detection and management, Table 3. Schedule of Activities, Footnote n and Footnote t were updated.

n.	The dose of LAM-003 will be administered to the subject in the study center (with recording of the date and actual clock time of the LAM-003 administration). On C1D2, C1D3, C1D4, and C1D5, LAM-003 should only be administered after the serum chemistry results from that day have been evaluated to exclude Grade 4 TLS or Grade 3 TLS associated with Grade >2 renal dysfunction or other Grade >2 end-organ injury ~~TLS~~.
t.	Serum chemistry studies to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, ALP, CK, LDH, total bilirubin, uric acid. Serum chemistry studies should be performed once on each designated day. On C1D2, C1D3, C1D4, C1D5, serum chemistry results from that day should be evaluated for evidence of Grade 4 TLS or Grade 3 TLS associated with Grade >2 renal dysfunction or other Grade >2 end-organ injury ~~to exclude TLS~~ before the subject is administered LAM-003 in the clinic. On C1D15 and C2D15, serum chemistry studies may be obtained at a local laboratory.

Changes to: 8 Safety Assessments, 8.4 Grading of the Severity of an Adverse Event

Changes/Rationale: Given the expectation that study sites would report changes in the severity of AEs, a limitation was removed that sites were to report only the highest severity grade for an AE.

The severity of AEs will be graded and reported using the CTCAE, Version 4.03 [NCI 2010]. ~~For each episode, the highest severity grade attained should be reported.~~

(No change to Paragraphs 2 or 3, or to Table 4)

14.8 Summary of Changes to Protocol – Amended Version 4

14.8.1 Overview of Changes

The modifications from Version 3 to Version 4 of the protocol included the following:

- Information regarding a comparative toxicology study of LAM-003 and LAM-003A in rats was added to the protocol introduction section.
- The enrollment procedures were clarified to indicate that study candidates could be rescreened if such rescreening was medically appropriate and was approved by the medical monitor.
- The minimum FLT3-ITD mutant-to-WT allele ratio cutoff allowing subject enrollment to the study was lowered from >0.40 to ≥0.05 and it was explicitly indicated that either peripheral blood or bone marrow could be used to evaluate subject elegibility.
- It was clarified that a leukemic blast cell count >50 × 10^9/L in the peripheral blood could be the basis for a study candidate exclusion from study participation.
- Descriptions were included of the specific tests to be performed during ophthalmological evaluations.
- Enrollment criteria text was corrected to indicate that study candidates likely to receive strong CYP3A4 inhibitors or inducers chronically be excluded from study participation. Relevant supportive care text was corrected, and the associated appendix table was updated to describe strong CYP3A4 inhibitors and inducers based on the most recent listing of such drugs in FDA guidance.
- It was clarified that a peripheral blood sample and/or a bone marrow aspirate sample could be submitted for confirmation of FLT3-ITD mutation status.

14.8.2 Specific Changes

In preparing Amended Version 4 of the protocol document, the following specific changes were made. Explanations of the changes are provided in italics as "***Changes/Rationale***". Inserted text is indicated by double-underlining. Deleted text is indicated by ~~strikeout~~. Revisions to the synopsis are not described. Changes to protocol versions and dates, modifications to the list of abbreviations and definitions of terms, routine bibliographic reference updates, or minor typographical or syntax corrections are not indicated.

Changes/Rationale: Information regarding a comparative toxicology study of LAM-003 and LAM-003A in rats was added to the protocol introduction section.

Changes to: Section 1 INTRODUCTION, 1.4 LAM-003/LAM-003A, 1.4.3 Nonclinical Experience, 1.4.3.4 General Toxicology

In support of clinical development in patients with cancers, LAM-003A underwent toxicological evaluation in conformance with the International Conference on Harmonization (ICH) S9 guidance on nonclinical assessments of anticancer pharmaceuticals [FDA 2010]. This evaluation included 28-day and 16-week GLP toxicology studies in rats and monkeys that formed the central basis for Phase 1, first-in-human dose selection and clinical safety monitoring. In addition, a 28-day study compared the toxicology and toxicokinetics of LAM-003 and LAM-003A in rats.

Changes to: Section 1 INTRODUCTION, 1.4 LAM-003/LAM-003A, 1.4.3 Nonclinical Experience, 1.4.3.4 General Toxicology, 1.4.3.4.5 Comparative Repeat-Dose Study of LAM-003 and LAM-003A

1.4.3.4.5 Comparative Repeat-Dose Study of LAM-003 and LAM-003A

This study was conducted to evaluate the potential toxicity and toxicokinetics of LAM-003 and LAM-003A in rats when administered orally for 28 days followed by a 14-day recovery period Two groups of Sprague-Dawley rats were administered LAM-003 at dose levels of 67 and 134 mg/kg/day (respective molar equivalent doses of 50 and 100 mg/kg/day of LAM-003A). One group of animals was administered LAM-003A at a dose level of 100 mg/kg/day (the NOAEL of LAM-003A in a previous study). One additional group of animals was administered vehicle. Following 28 days of administration, recovery animals were maintained for a 14-day recovery period.

No early deaths occurred. A lower body weight gain was observed in males given 100 mg/kg/day LAM-003A and in males given 134 mg/kg/day LAM-003 during the dosing period. Further loss was not observed during recovery. No effects on food consumption or changes in ophthalmology were noted in any group.

Minimal to mild decreases in lymphocytes, eosinophils, basophils and platelets were observed in both sexes receiving 134 mg/kg/day LAM-003 and 100 mg/kg/day LAM-003A. The changes were similar in magnitude between animals receiving LAM-003 and LAM-003A. Minimal increases in serum AST and ALT were observed at termination in both sexes given 100 mg/kg/day LAM-003A. Although these changes were considered related to treatment, they were not considered biologically relevant based on their small magnitude and/or and lack of histopathologic correlates. These changes had resolved by the recovery interval.

Spleen and thymus weights were decreased in both sexes at 67 and 134 mg/kg/day of LAM-003 and at 100 mg/kg/day LAM-003A. Similar microscopic findings were observed in rats given LAM-003 or LAM-003A orally for 28 days, including minimal to mild cortical lymphoid necrosis and/or minimal to mild generalized lymphoid depletion of the thymus; minimal to mild mixed depletion of the bone marrow; and minimal edema, minimal hyperkeratosis, minimal epithelial hyperplasia and/or mild erosion/ulceration of the stomach in both sexes, primarily in the high dose groups (100 mg/kg/day equimolar dose). Minimal to moderate physeal thickening was observed in the growth plate of the femur in males in all LAM-003 and LAM-003A groups and minimal bilateral follicular cell hypertrophy in the thyroid gland was observed in females in the high-dose groups. All findings generally resolved during the recovery period. There were no toxicities observed in animals given LAM-003 that were not also observed in animals given equimolar doses of LAM-003A.

Changes/Rationale: The enrollment procedures were clarified to indicate that study candidates could be rescreened if such rescreening was medically appropriate and was approved by the medical monitor.

Changes to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.4 Enrollment and Replacement of Study Subjects

Inclusion and exclusion criteria will be reviewed for each potential subject by qualified study center personnel. If the consented study candidate is considered eligible for study participation, the study center will transmit a study-specific eligibility and enrollment form to LAM (or designee). If medically appropriate, study candidates who do not initially meet screening criteria may be rescreened with the approval of the medical monitor.

(No changes to Paragraphs 2 or 3)

Changes/Rationale: Based on discussions with the investigators, it was elected to decrease the minimum FLT3 mutant-to-WT allele ratio cutoff allowing subject enrollment to the study from >0.40 to ≥0.05 and permit diagnosis based on peripheral blood or bone marrow.

Changes to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.1 Inclusion Criteria, Inclusion Criterion 3

3. Current d~~D~~iagnosis of FLT3-ITD-mutant AML (with a mutant-to-WT allele ratio of ~~>0.40~~≥0.05 in peripheral blood or bone marrow at screening as documented by the LeukoStrat® CDx FLT3 mutation assay).

Changes/Rationale: It was clarified that a leukemic blast cell count >50 × 10^9/L in the peripheral blood could be the basis for a study candidate exclusion from study participation.

Changes to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.2 Exclusion Criteria, Exclusion Criterion 16

1. Peripheral blood l~~L~~eukemic blast cell count >50 × 10^9/L before the start of study therapy and despite the use of hydroxyurea.

Changes/Rationale: Descriptions were included of the specific tests to be performed during ophthalmological evaluations.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.3 Supportive Care, 6.3.13 Ophthalmological Symptom Management

(No change to Paragraph 1)

During the study, subjects will undergo screening and periodic ophthalmological examinations (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography~~eg, visual acuity testing, electroretinography, and slit lamp examination~~) according to the schedule of activities provided in Section 7. As noted in Section 6.2.7, subjects who develop treatment-emergent dose-limiting visual symptoms should have drug interrupted and should undergo more frequent ophthalmological consultation (eg, at ~2-week intervals or more frequently, as appropriate). Symptoms should resolve to Grade ≤1 before resumption of study drug and study drug should only be resumed if such resolution occurs within 2 weeks of interruption of study drug and the subject appears to be otherwise safely benefiting from study therapy.

Changes to: 7 Study Activities and Assessments, Table 3, Footnote l.

l. Ophthalmologic evaluations (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography~~eg, with visual acuity testing, electroretinography, slit lamp examination~~) should be performed by an ophthalmologist during Screening, within 14 days before C2D1, within 14 days before C4D1 (8-week interval), and then within 14 days before C7D1, C10D1, C13D1, C16D1, etc (12-week intervals), and at End-of-Therapy

Changes to: 9 LABORATORY AND OTHER ASSESSMENTS, 9.1 Methods and Analytes

(No change to Paragraphs 1-7, 9 or 10)

Ophthalmological examinations should be performed by a consulting ophthalmologist or optometrist with the necessary facilities and equipment to perform appropriate testing (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography~~eg, visual acuity testing, electroretinography, slit lamp examination~~); interpretations of ophthalmological findings will be provided by a consulting ophthalmologist.

Changes to: 9 LABORATORY AND OTHER ASSESSMENTS, 9.1 Methods and Analytes, Table 8

Ophthalmology examination	• Examination by an ophthalmologist or optometrist (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography~~eg, visual acuity testing, electroretinography, slit lamp examination~~)

Changes/Rationale: Erroneous text was present indicating that study candidates likely to receive moderate or strong CYP3A4 inhibitors or inducers would be excluded from study participation. It was intended that only study candidates likely to receive strong CYP3A4 inhibitors or inducers chronically be excluded from study participation. Accordingly, the text in the relevant exclusion criterion was corrected, supportive care text was corrected, the relevant appendix was updated to describe only strong CYP3A4 inhibitors and inducers, and a more recent reference was included in support of the appendix table.

Changes to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.2 Exclusion Criteria, Exclusion Criterion 16

16. Use of a strong inhibitor or inducer of cytochrome P450 (CYP) 3A4 (including itraconazole, ketoconazole, posaconazole, or voriconazole) within 7 days prior to the start of study therapy or expected requirement for chronic use of a ~~moderate or~~ strong CYP3A4 inhibitor or inducer during Cycle 1 of study therapy (see Appendix 14.4). ***Note: For subjects requiring antifungal prophylaxis/therapy, oral fluconazole or isavuconazonium can be considered. Echinocandins (eg, caspofungin, anidulafungin, or micafungin) are also acceptable, realizing the disadvantage of the requirement for intravenous administration***.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.3 Supportive Care, 6.3.2 Antibiotics, Antifungals, and Antivirals

Local practices or guidelines regarding infection prophylaxis may be followed. Subjects developing an intercurrent infection during study drug treatment may receive therapeutic antibacterial, antiviral, or antifungal drugs as needed. However, care should be taken to avoid or minimize concomitant administration of prophylactic or therapeutic antibacterial, antifungal, or antiviral, agents that are ~~moderate or~~ strong CYP3A4 inhibitors or inducers (see Section 6.3.9 and Appendix 14.4). Continuation of study therapy during treatment for an intercurrent infection is at the discretion of the investigator.

Changes to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.3 Supportive Care, 6.3.9 Drugs with Drug-Drug Interaction Potential

(No change to Paragraphs 1,2, 3, or 4)

For subjects who require temporary use of a drug that does affect these enzymes (eg, treatment with a systemic antifungal agent), LAM-003 therapy can be temporarily interrupted and then resumed after completion of the other drug. For subjects who require initiation of chronic therapy with a drug that ~~moderately or~~ strongly affects these enzymes, investigators must consult with the medical monitor to consider the best course of action. If subjects do receive a CYP3A4 inhibitor concomitantly with LAM-003, they should be monitored closely for signs of LAM-003 toxicity. Based on consultation with the medical monitor, such subjects may be required to undergo additional pharmacokinetic testing and may require a LAM-003 dose modification.

Changes to: Section 14 APPENDICES, 14.4 Strong Inhibitors or Inducers of CYP3A4

14.4 Strong ~~Potent~~ Inhibitors and Inducers of CYP3A4

~~Effect on CYP3A~~	~~Drug Class~~	~~Medications~~
~~Moderate to Strong CYP3A Inhibitors~~	~~Antibiotics~~	~~chloramphenicol, ciprofloxacin, clarithromycin, erythromycin, telithromycin~~
	~~Antiemetic~~	~~aprepitant~~
	~~Antifungals~~	~~ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole~~
	~~Antiviral protease inhibitors~~	~~amprenavir, atazanavir, boceprevir, cobicistat, darunavir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir~~
	~~Calcium-channel blockers~~	~~diltiazem, mibifradil, verapamil~~
	~~Foods/herbs~~	~~grapefruit, grapefruit juice, Seville oranges~~
	~~Serotonin antagonist~~	~~nefazodone~~
	~~Tyrosine kinase inhibitor~~	~~imatinib~~
	~~Vasopressin antagonist~~	~~conivaptan~~
~~Moderate to Strong CYP3A Inducers~~	~~Antibiotics~~	~~nafcillin, rifampin~~
	~~Anticonvulsants~~	~~carbamazepine, phenobarbital, phenytoin~~
	~~Antiviral reverse transcriptase inhibitors~~	~~efavirenz, etravirine~~
	~~Endothelin receptor antagonist~~	~~bosentan~~
	~~Foods/herbs~~	~~St. John's wort~~
	~~Wakefulness-promoting agent~~	~~modafinil~~

~~**Reference:** [FDA 2016]~~
~~**Abbreviation:** CYP=cytochrome P450 enzyme~~

Effect on CYP3A	Drug
Strong CYP3A Inhibitors	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavi), grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole
Strong CYP3A Inducers	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

Abbreviation: CYP=cytochrome P450 enzyme
Reference: [FDA 2017]

Changes to: Section 13 BIBLIOGRAPHY

~~FDA (Food and Drug Administration). Drug development and drug interactions: table of substrates, inhibitors and inducers. 2016 Sep 27. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (accessed 2017 Sep 20).~~

Food and Drug Administration (FDA). Drug development and drug interactions: Table of substrates, inhibitors and inducers. 2017 Nov 14. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4 (accessed 2018 June 11).

Changes/Rationale: The Schedule of Activities was clarified to indicate that a peripheral blood sample and/or a bone marrow aspirate sample could be submitted for confirmation of FLT3-ITD mutation status.

Changes to: Section 7 STUDY ACTIVITIES AND ASSESSMENTS, Table 3

Body of Table 3

Blood and/or bone marrow for FLT3-ITD mutation [dd]

Footnote of Table 3

cc. Blood and/or bone marrow aspirate for FLT3-ITD mutation confirmation in AML blasts using the LeukoStrat® CDx FLT3 mutation assay will be obtained during Screening.

14.9 Summary of Changes to Protocol – Amended Version 5

14.9.1 Overview of Changes

The modifications from Version 4 to Version 5 of the protocol included the following:

- Based on discussions with study investigators, it was noted that study candidates who had undergone HSCT could have persistent need for systemic corticosteroids for low-grade GVHD and that such corticosteroid use was precluding participation in the study. Because there was no specific safety, efficacy, or drug-drug interaction concern regarding coadministration of LAM-003 and corticosteroids, the protocol was modified in 2 ways:
    - It was specified that study candidates with high-grade GVHD would be excluded from the study.
    - It was indicated that study candidates who had completed other immunosuppressive therapy but required continued corticosteroids would not be excluded from protocol participation.
    - Other sections of the protocol describing corticosteroid use were modified in accordance with the changes to the enrollment criteria.

14.9.2 Specific Changes

In preparing Amended Version 5 of the protocol document, the following specific changes were made. Explanations of the changes are provided in italics as "***Changes/Rationale***". Inserted text is indicated by double-underlining. Deleted text is indicated by ~~strikeout~~. Revisions to the synopsis are not described. Changes to protocol versions and dates, modifications to the list of abbreviations and definitions of terms, routine bibliographic reference updates, or minor typographical or syntax corrections are not indicated.

Changes/Rationale: It was specified that study candidates with high-grade GVHD would be excluded from the study based on disease manifestations rather than based on use of immunosuppressive drugs.

Change to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.2 Exclusion Criteria, Exclusion Criterion 12

12. In subjects with prior HSCT, evidence of graft-versus-host disease (GVHD) manifesting as NCI CTCAE Version 4.03 Grade >2 serum bilirubin, Grade >3 skin involvement, or Grade >3 diarrhea at ~~requiring immunosuppressive therapy within 4 weeks prior to~~ the start of study therapy.

Changes/Rationale: It was indicated that study candidates who had completed other immunosuppressive therapy but required continued corticosteroids would not be excluded from protocol participation. Text relating to incidental use of intraarticular corticosteroids was also incorporated.

Change to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.2 Exclusion Criteria, Exclusion Criterion 15

15. Ongoing immunosuppressive therapy other than corticosteroids~~, including systemic or enteric corticosteroids~~. ***Note: At study entry, subjects may be using systemic, intraarticular, inhaled, or topical corticosteroids. During study therapy, subjects may use systemic, enteric, intraarticular, inhaled, or topical corticosteroids as required for intercurrent conditions.***

Changes/Rationale: Text in this section was modified in accordance with the changes to the enrollment criteria.

Change to: Section 5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.6 Rationale for Subject Selection

(No change to Paragraphs 1,2, 3, 4, or 6)

Exclusion of subjects who have undergone prior HSP inhibitor therapy is intended to avoid enrolling subjects with AML that is likely to be resistant to LAM-003. Avoidance of concomitant ~~corticosteroid therapy~~ immunosuppressives at baseline minimizes the potential that such therapy would depress the potential immunotherapeutic effects of LAM-003 or confound adequate profiling of the LAM-003 safety profile. Restrictions on concomitant administration of CYP3A4 inhibitors are important because in vitro data suggest that LAM-003A is primarily metabolized by CYP3A4 (see Section 1.4.3.3). Exclusions for cardiac waveform or rhythm

abnormalities are intended to ensure that subjects do not have conduction system disorders that would increase risk or confound on-study ECG evaluations.

Changes/Rationale: Text in this section was modified in accordance with the changes to the enrollment criteria.

Change to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORTIVE CARE, 6.3 Supportive Care, 6.3.6 Antiemetics

(No change to Paragraphs 1,2, 3, 4, or 5)

~~Use of systemic corticosteroids (eg, dexamethasone) should be minimized to avoid interference with the potential immunopotentiating effects of study therapy; however, c~~ Corticosteroids can be introduced if other types of antiemetic agents are not sufficiently effective.

Changes/Rationale: Text in this section was modified in accordance with the changes to the enrollment criteria.

Change to: Section 6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORTIVE CARE, 6.3 Supportive Care, 6.3.8 Corticosteroids

At study entry, subjects may ~~not~~ be using systemic, intraarticular, ~~or enteric corticosteroids but may be receiving~~ inhaled, or topical corticosteroids. During study therapy, subjects may use systemic, intraarticular, enteric, inhaled, or topical ~~or enteric~~ corticosteroids as required for ~~treatment-emergent~~ intercurrent conditions.

14.10 Summary of Changes to Protocol – Amended Version 6

14.10.1 Overview of Changes

The modifications from Version 5 to Version 6 of the protocol included the following:

- The protocol had originally focused on enrolling only patients with FLT3-ITD AML. However, this restriction was constraining accrual to the study. Because nonclinical data indicate that LAM-003 has the potential for activity in patients with FLT3-ITD, FLT3-TKD, and FLT3-WT AML, it was elected to expand accrual to permit enrollment of patients with any of these forms of AML. The change was endorsed by study investigators and conformed with a suggestion from the FDA at the time of opening the LAM-003 IND. As a consequence of this study modification, the type of screening testing was altered and the requirement that study candidates must have previously received FLT3 kinase inhibitors was removed.
- At the request of the investigators, the protocol was modified to allow use of any of hydroxyurea, cytarabine, or cyclophosphamide to control blast count proliferation during Cycle 1.
- To conserve supplies of study drug, modifications were made to the dispensing instructions.
- To encourage adequate review of the subject dosing diary by site personnel, additional instructions regarding dosing diary review and documentation were included in protocol text.
- To encourage collection of historical data regarding AML genetic profiling, instructions for acquisition of this information were included in the protocol.

14.10.2 Specific Changes

In preparing Amended Version 6 of the protocol document, the following specific changes were made. Explanations of the changes are provided in italics as "***Changes/Rationale***". Inserted text is indicated by double-underlining. Deleted text is indicated by ~~strikeout~~. Revisions to the synopsis are not described. Changes to protocol versions and dates, modifications to the list of abbreviations and definitions of terms, routine bibliographic reference updates, or minor typographical or syntax corrections are not indicated.

Changes/Rationale: The protocol had originally focused on enrolling only patients with FLT3-ITD AML. However, this restriction was constraining accrual to the study. Because nonclinical data indicate that LAM-003 has the potential for activity in patients with FLT3-ITD, FLT3-TKD, and FLT3-WT AML, it was elected to expand accrual to permit enrollment of patients with any of these forms of AML. The change was endorsed by study investigators and conformed with a suggestion from the FDA at the time of opening the LAM-003 IND. As a consequence of this study modification, the type of screening testing was altered and the requirement that study candidates must have previously received FLT3 kinase inhibitors was removed.

1 INTRODUCTION, 1.3 Heat Shock Proteins as Clinical Targets for AML Therapy, 2nd Paragraph

Mutant FLT3~~-ITD-~~ is a client protein of HSP90 [Minami 2002, Yao 2003, Al Shaer 2008]. Mutant FLT3~~FLT3-ITD-~~ expression is associated with higher levels of HSP90 expression in primary AML cells [Reikvam 2011]. Treatment with an HSP90 inhibitor induces mutant FLT3-~~ITD-~~ degradation and tumor cytotoxicity [Yao 2003, Zong 2015], leading to enhanced sensitivity of AML blasts harboring this oncogenic mutation [Zong 2015].

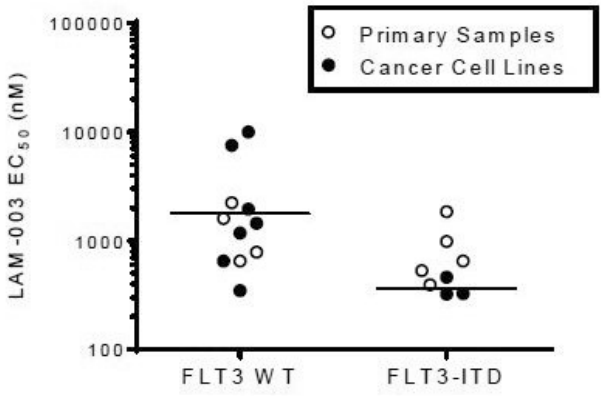
1 INTRODUCTION, 1.4 LAM-003/LAM-003A, 1st Paragraph

Based on the collective knowledge regarding the roles of FLT3 and HSP90 in AML, LAM Therapeutics, Inc (LAM) is developing LAM-003 as a clinical HSP90 inhibitor for patients with ~~FLT3-ITD-mutant-~~ AML. The initial goal of development is to offer a novel treatment approach that can circumvent ~~FLT3-ITD~~resistance in patients who have experienced failure of ~~FLT3 inhibitors~~ other drugs. Ultimately, it is hoped that LAM-003 administered alone or in combination can supplement or complement current treatment methods.

1 INTRODUCTION, 1.4 LAM-003/LAM-003A, 1.4.3 Nonclinical Experience, 1.4.3.1 Efficacy Pharmacology, 1.4.3.1.1 in Vitro Studies, 1st, 2nd, and 5th Paragraphs

In vitro studies indicated that LAM-003 demonstrates mutant FLT3~~-ITD~~ client protein degradation and preferential cytotoxicity toward AML cell lines and primary AML cells harboring a FLT3-ITD mutation (Figure 3); in these experiments, the geometric mean EC_{50} values were 576 nM for FLT3-ITD-mutant cells (n=8) vs 1525 nM for FLT3-wild-type (WT) cells (n = 11). However, as also shown in (Figure 3), multiple FLT3-WT AML cell lines and patient-derived tumors share the enhanced sensitivity to LAM-003 displayed by FLT3-ITD AML cells in vitro.

Figure 3: LAM-003 Demonstrates Potent Antileukemic Activity in AML Cells



Abbreviation: AML=acute myeloid leukemia, EC_{50}=median effective concentration, FLT3=FMS-like tyrosine kinase 3, ITD=internal tandem duplication, WT=wild type

To further characterize the ability of LAM-003 to cause FLT3-mutant degradation, testing was performed on BaF3 murine cells made dependent on several oncogenic FLT3 mutations (including: FLT3-WT, FLT3-ITD, FLT3 D835V, FLT3-ITD D835V, FLT3 D835Y, FLT3-ITD D835Y, FLT3 D835H, FLT3-ITD D835H, FLT3 F691L, and FLT3-ITD F691L). As assessed by flow cytometry, LAM-003 caused similar dose-dependent reductions in FLT3 cell surface expression on all mutant cell lines but had relatively little effect on BaF3 cells expressing a FLT3-WT receptor. By this measure, FLT3-TKD mutants are as sensitive to LAM-003 degradation as FLT3-ITD mutations.

T-cell-derived interferon gamma (IFNγ) has been shown to induce the protein expression of programmed death-ligand 1 (PD-L1) in a variety of cancer cell types, thus providing a mechanism by which tumor cells can evade immune detection. To test whether LAM-003 can block IFN-γ-induced PD-L1 expression, 6 primary AML samples (FLT3-WT, n=2; FLT3-ITD, n=4) were treated with human IFNγ alone, LAM-003 alone, or a combination of IFNγ and LAM-003 for 24 hours. At this timepoint, LAM-003 did not affect the viability of the AML blasts. Samples from all patients responded to IFNγ treatment by increasing the amount of PD-L1 on the cell surface (5- to 25-fold). LAM-003 alone did not affect basal PD-L1 cell surface protein. However, when combined with IFNγ, LAM-003 significantly reduced IFNγ-induced PD-L1 cell surface expression. These data show that, in addition to possessing cytotoxic activity against AML ~~FLT3-ITD~~, LAM-003 may also possesses salutary immunopotentiating activity.

1 INTRODUCTION, 1.5 Conclusions, 1st and 4th Bullet Points

The conduct of this Phase 1 study of LAM-003 in patients with AML is founded on a current understanding of the natural history and current therapies for patients with this malignancy; knowledge of the importance of FLT3 and HSP90 cellular pathways in the pathophysiology of this disease; and nonclinical and clinical information regarding the efficacy and safety of LAM-003 and LAM-003A. The collective data support the following conclusions:

- Relapsed or refractory AML is a serious, disabling, and life-threatening disorder. Existing therapies can induce complete tumor regressions but often lose effectiveness over time. Through its effects as an HSP90 inhibitor and immunopotentiator, LAM-003 offers the potential for overcoming disease resistance and improving clinical outcomes for patients with previously treated ~~FLT3-ITD-mutant~~ AML.
- Clinical evaluation of LAM-003 in patients with AML has sound scientific rationale based on evaluation of its therapeutic potential in in vitro and in vivo models relevant to human leukemia.
- Advancing the development of LAM-003 in this study is well supported by nonclinical evaluations of LAM-003 and LAM-003A pharmacology, pharmacokinetics, and toxicology and by Phase 1 assessment of the safety and pharmacokinetics of LAM-003A in patients with solid tumors. This collective information provides a basis for subject enrollment criteria; starting dose selection and dose escalation; administration of an appropriate dosing regimen and supportive care; and for safety, pharmacodynamic, pharmacokinetic, and efficacy monitoring within this study.
- Given the seriousness of previously treated, progressive AML and the aggregate potential benefits considered in the context of potential risks, clinical development of LAM-003 in patients with ~~FLT3-ITD-mutant~~ AML is justified.

The rationale for specific design features of the study is provided in relevant sections of the protocol, including Section 2.3 (Rationale for Study Design), Section 4.3 (Rationale for Selection of Endpoints), Section 5.6 (Rationale for Subject Selection), and Section 6.6 (Rationale for Study Drug Administration and Supportive Care).

2 STUDY DESIGN AND CONDUCT, 2.2 Study Design

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 ~~FLT3-ITD-mutant~~ AML. Subjects will self-administer oral LAM-003 QD or BID continuously in repeated 28-day cycles. Cohorts of 3 to 6 subjects will be sequentially enrolled at progressively higher dose levels of LAM-003 using a standard 3+3 dose-escalation design. Based on the pattern of DLTs observed in Cycle 1, escalation will proceed to define an MTD and a recommended dosing regimen (RDR) that may be at the MTD or a lower dose within the tolerable dose range.

3 STUDY OBJECTIVES, 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 ~~FLT3-ITD-mutant~~ AML receiving LAM-003

4 STUDY ENDPOINTS, 4.2 Secondary Endpoints, 4.2.4 Exploratory Endpoints, 4.2.4.1 Pharmacodynamics, 1st Bullet

- Changes in FLT3~~-ITD~~ 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)

4 STUDY ENDPOINTS, 4.2 Secondary Endpoints, 4.2.4 Exploratory Endpoints, 4.2.4.2 Biomarkers

- Baseline AML blast FLT3 mutation type and FLT3~~-ITD~~ mutation-to-WT allele ratio ~~(as evaluated using the LeukoStrat® CDx FLT3 mutation assay)~~

4 STUDY ENDPOINTS, 4.3 Rationale for Selection of Endpoints, 7th Paragraph

Changes in FLT3~~-ITD~~ expression, FLT3 pathway activation, HSP protein and gene expression, and PD-L1 expression in AML blasts are assessed during C1 therapy to provide evidence of drug mechanism, offer context for efficacy findings, and assist in final dose and schedule selection. Changes in plasma FL concentrations are intended to provide information that may corroborate drug effects on cellular alterations in FLT3. Immunophenotyping assays for changes in circulating B-cell, T-cell, NK cell, and monocyte subsets will characterize the peripheral immune status of the subject and any possible LAM-003 effects on these parameters. Baseline evaluations of FLT3 and overall mutational status in AML blasts are intended to generate subject selection hypotheses for future studies.

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.1 Inclusion Criteria, Criteria 3 and 5

3. Current diagnosis of ~~FLT3-ITD-mutant~~ AML ~~(with a mutant-to-wild-type allele ratio of ≥0.05 in peripheral blood or bone marrow at screening as documented by the LeukoStrat® CDx FLT3 mutation assay)~~.

~~5. Prior treatment for AML has included ≥1 regimen containing a FLT3 kinase inhibitor (eg, midostaurin, sorafenib, lestaurtinib, quizartinib, crenolanib, or gilteritinib) given as monotherapy or in combination.~~

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.6 Rationale for Subject Selection, 3rd Paragraph

~~A fundamental premise of the study is that LAM-003 HSP90 inhibition will cause degradation of ITD-mutated FLT3 in patients who have become resistant to existing FLT3 inhibitors. Accordingly, subjects must have a current diagnosis of FLT3-ITD-mutant AML and have undergone prior therapy with a FLT3 kinase inhibitor (eg, midostaurin, sorafenib, lestaurtinib quizartinib, crenolanib, or gilteritinib).~~ The requirement for the presence of AML that is measurable ensures that subjects have disease that can be fully assessed for evidence of drug efficacy.

7 STUDY ACTIVITIES AND ASSESSMENTS, Table 3, Body of Table and Footnotes

Blood for AML FLT3~~-ITD~~/HSP protein expression [x]
x. Blood for FLT3~~-ITD~~/HSP protein expression in AML blasts will be collected on C1D1 (predose and 8 hours postdose), C1D2 (24 hours postdose/predose for next drug administration), C1D8 (predose and 8 hours postdose), and C2D1.

Blood and/or bone marrow for FLT3~~-ITD~~ mutation [dd]
x. Blood and/or bone marrow aspirate for FLT3~~-ITD~~ mutation confirmation in AML blasts using a sponsor-specified ~~the LeukoStrat® CDx FLT3 mutation~~ assay will be obtained during Screening.

ee. Blood for peripheral blood AML blast count evaluation and bone marrow aspiration/biopsy will be performed during Screening (unless the requirement for screening bone marrow aspirate/biopsy is waived by the medical monitor because sufficient bone marrow material is available for response determination). Post-baseline, a bone marrow aspirate/biopsy is required within 14 days before C3D1, C5D1, C7D1 (8-week intervals), and then within 14 days before C10D1, C13D1, C16D1, etc (12-week intervals). An End-of-Therapy bone marrow aspirate/biopsy should be performed unless the subject already has hematological or radiographic confirmation of DRP ≤8 weeks before permanent study drug discontinuation. At all AML evaluations, the extent of involvement with AML in peripheral blood and bone marrow, the presence of Auer rods, and bone marrow cellularity will be assessed. Bone aspirate aliquots obtained at Screening and within 14 days before C3D1 may also be evaluated for FLT3~~-ITD~~/ HSP protein and gene expression, PD-L1, and AML mutations.

9 LABORATORY AND OTHER ASSESSMENTS, 9.1 Methods and Analytes, 5th Paragraph, and Body of Table 8.

FLT3 mutation analysis in AML blasts using ~~the LeukoStrat® CDx~~a FLT3 mutation assay will be performed at LAM or at a LAM-designated contract laboratory.

Peripheral blood and bone marrow aspirate cellular pharmacodynamics	• FLT3~~-ITD~~ 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) • HSP gene expression in AML blasts (as measured using quantitative PCR) • PD-L1 expression in AML blasts (as measured using flow cytometry)

Peripheral blood or bone marrow cellular AML FLT3~~-ITD~~ mutation analysis	• Peripheral blood or bone marrow AML blast FLT3 mutation type and FLT3~~-ITD~~ mutation-to-WT allele ratio (as evaluated using a sponsor-specified ~~the LeukoStrat® CDx~~ FLT3 mutation assay)

11 Statistical Considerations, 11.2 Analysis Plan, 11.2.1 Subject Disposition and Baseline Characteristics, 2nd Paragraph

Subject baseline characteristics (eg, subject demographics, medical history, disease history, prior therapy, FLT3~~-ITD~~ mutational status and mutant-to-WT allele ratio, peripheral AML blast count, bone marrow blast percentage, peripheral blood ANC, peripheral blood platelet count, peripheral blood hemoglobin, baseline TLS risk status, etc) will be listed and summarized for the full analysis set.

Changes/Rationale: At the request of the investigators, the protocol was modified to allow use of any of hydroxyurea, cytarabine, or cyclophosphamide to control blast count proliferation during Cycle 1.

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.1 Inclusion Criteria, Criterion 7 (Now Criterion 6)

7. All acute toxic effects of any prior antitumor therapy (except hydroxyurea, cytarabine, and/or cyclophosphamide given to control blast count proliferation) resolved to Grade ≤1 before the start of study therapy (with the exception of alopecia [Grade ≤2 permitted], neurotoxicity [Grade ≤2 permitted], or bone marrow parameters [Grade 1 to 4 permitted]). ***Note: For subjects with rapidly proliferative disease, use of hydroxyurea, cytarabine, and/or cyclophosphamide is allowed before the start of study therapy and during Cycle 1, but must be discontinued thereafter.***

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5 Subject Selection Criteria, 5.5.2 Exclusion Criteria, Criterion 1

1. Peripheral blood leukemic blast cell count >50 × 109/L before the start of study therapy and despite the use of hydroxyurea, cytarabine, and/or cyclophosphamide.

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.3 Supportive Care, 6.3.3 Anticancer Therapies Other than the Study Drugs

Other than hydroxyurea, cytarabine, and/or cyclophosphamide used during Cycle 1 to control AML blast counts, no~~No~~ systemic anticancer therapies (including chemotherapy, antibody therapy, hormonal therapy, immunotherapy, radiotherapy, or other experimental therapies) for the subject's cancer are permitted while the subject is receiving study treatment. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

7 STUDY ACTIVITIES AND ASSESSMENTS, Table 3, Footnote c

c.	Concomitant medication assessments should include information regarding all prescription, nonprescription, illicit, and alternative medications (health foods). Use of any supportive care (eg, antiproliferative drugs, antidiarrheals, antiemetics, hematopoietic growth factors, transfusions) should be noted. On C1D15 and C2D15, concomitant medication information may be obtained via telephone contact with the subject.

Changes/Rationale: To conserve supplies of study drug, modifications were made to the dispensing instructions.

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.1.5 Dispensing, 1st Paragraph

A pharmacist or other qualified staff member will dispense bottles containing LAM-003 tablets. Sufficient bottles will be dispensed to the subject to provide an adequate drug supply until the subject's next planned clinic visit at which drug will be dispensed (generally at 28-day intervals). If it is anticipated that a subject may have a potential delay in returning to the study center (eg, due to a holiday), an ~~One~~ additional bottle may ~~should~~ be provided at the start of therapy so that the subject has an overage supply to cover any potential delays in returning to the study center. Sites should take care to minimize waste.

Changes/Rationale: To encourage adequate review of the subject dosing diary by site personnel, additional instructions regarding dosing diary review and documentation were included in protocol text.

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.1.6 Return and Compliance Assessment

At the completion of each dispensing interval, empty, partially used, or full bottles of LAM-003 should be retrieved from the subject. The quantities of unused LAM-003 and the date when these study supplies are returned by the subject should be recorded in the study drug accountability records. In addition, ~~and~~ the subject's dosing diary should be reviewed at each visit, any incomplete or inconsistent entries should be addressed, and the dosing diary should be photocopied. Returned bottles may be redispensed to the same subject but not to another subject. Returned tablets and bottles may be destroyed according to the site's standard operating procedures (see Section 12.11).

7 STUDY ACTIVITIES AND ASSESSMENTS, Table 3, Body of Table and Footnote p

LAM-003 return/compliance and diary check [p]

p. Empty, partially used, or full bottles of LAM-003 will be retrieved from the subject and drug compliance will be assessed. In addition, the subject's dosing diary should be reviewed, any incomplete or inconsistent entries should be addressed, and the dosing diary should be photocopied.

Changes/Rationale: To encourage collection of historical data regarding AML genetic profiling, instructions for acquisition of this information were included in the protocol.

7 STUDY ACTIVITIES AND ASSESSMENTS, Table 3, Body of Table and Footnote cc

AML genetic profiling data from records [cc]

cc. Any available information in medical records regarding AML genetic profiling (eg, for FLT3 mutation status) to be collected for sponsor review.

9 LABORATORY AND OTHER ASSESSMENTS, 9.1 Methods and Analytes, 6th Paragraph

Any available information in the subject medical records regarding AML genetic profiling (eg, for FLT3 mutation status) will be provided in redacted format for sponsor review.

14.11 Summary of Changes to Protocol – Amended Version 7

14.11.1 Overview of Changes

The modifications from Version 6 to Version 7 of the protocol are summarized as follows:

- The introduction to the protocol was updated to document the expected LAM-003→LAM-003A conversion ratio and summarize the available clinical and pharmacokinetic experience with LAM-003 from this clinical trial; these changes were made to support the plan to evaluate additional LAM-003 dose levels.
- Information regarding the number of subjects to be accrued was modified consistent with other changes to the protocol.

- During accrual to the study, investigational sites had occasionally noted spuriously high values for cardiac QT interval when correcting with the Bazett formula (QTcB). These findings are consistent with published literature indicating that the QTcB tends to overestimate the QT interval and that correction using the Fridericia formula (QTcF) provides more accurate data in adults. In addition, the FDA had indicated that the QTcF alone is acceptable in analyzing QT data from clinical trials in adults. Based on these observations and considerations, it was elected to use only the QTcF value for purposes of establishing eligibility, determining DLT, assessing potential critical QT alerts, and statistical analyses.
- In post-marketing surveillance, rare instances of cardiac QT prolongation and ventricular dysrhythmias had been observed in patients taking fluconazole. For this reason, fluconazole was listed in Appendix 14.5 as a drug having a known association with QT prolongation and thus its use was proscribed per protocol. However, as documented in fluconazole product labeling, most of the case reports of increases in QT interval were limited to patients with confounding disease, drug, or electrolyte risk factors. Accordingly, the protocol was updated to indicate that concomitant use of fluconazole prophylaxis/therapy would be permitted in subjects enrolled to the study. Further, it was indicated that the medical monitor could sanction use of certain concomitant drugs if the risk of QT prolongation in a specific study subject was likely to be negligible.
- The exclusion criterion relating to participation in another therapeutic or imaging clinical trial was clarified.
- The need for documentation of the timing of LAM-003 administration in conjunction with frequent pharmacokinetic assessments was emphasized
- The definition of an overdose was changed to accommodate changes in the dose range of LAM-003 being explored in the study.
- Prior Phase 1 clinical dose ranging with the active LAM-003 metabolite, LAM-003A, established an MTD in the range of 480 mg/day to 600 mg/day. LAM-003A dosing was not limited by high-grade DLTs but by reversible low-grade nausea vomiting at doses >600 mg/day. In the current LAM-003 study, it was considered possible that administration of LAM-003 as a prodrug for LAM-003A might result in lower effective drug exposure at higher dose levels than was previously observed when administering the metabolite directly. LAM-003 administration in this study at dose levels of 200 mg QD and 300 mg QD demonstrated no discernable toxicity, justifying an increment in dose level to a planned 450 mg QD. Based on these considerations and the evolving LAM-003 safety profile, it was anticipated that exploration of higher LAM-003 dose levels might be warranted. Accordingly, it was elected to add LAM-003 dose levels of 600 mg (1.33-fold increment) and 750 mg QD (1.25-fold increment) to the dose escalation-scheme. Actual dose escalation continued using the existing 3+3 paradigm, DLT definitions, and safety monitoring; thus, all existing safety protections remained in place.

- Exploration of BID dosing was permitted per the existing protocol with the expectation that study subjects would receive divided doses that were half of the total daily dose in multiple of 50 mg (considering the 50-mg LAM-003 tablet size). The introduction of a potential total dose of 750 mg/day could result in unequal morning and evening dosing on a BID schedule. Thus, a provision for rounding up or down was introduced into the protocol (eg, 750 mg/day could be evaluated as 350 mg BID or 400 mg BID depending upon the emerging safety and pharmacokinetic profile of the drug).
- The requirement for a minimum period of 4 weeks of observation was made approximate to allow some latitude in the DLT observation period consistent with the allowed visit window (±3 days).
- Changes were incorporated into dose modification recommendations to maximize the potential for clinical benefit in individual subjects who proved to be tolerating therapy at a lower dose level and might safely benefit from a dose-escalation. In making these changes, safeguards were maintained: subjects must have tolerated therapy with no toxicities of Grade ≥2, only successive dose-level adjustments were permitted, the dose could not have exceeded an established MTD, the potential for additional monitoring was incorporated, and both the investigator and the medical monitor must have agreed that the dose escalation was medically appropriate.
- It was clarified that ophthalmological testing could be performed by ophthalmologists or optometrists but also by other specialists with the relevant expertise (eg, a neurologist for ERG testing).

  It was also noted that the medical monitor could approve omission of an End-of-Therapy ophthalmological evaluation; this change was implemented to provide some flexibility to deal with extenuating circumstance (eg, avoid repeat testing in a subject who had recently undergone ophthalmological testing or was too ill due to AML to be transported to the ophthalmology clinic).
- It was clarified that both peripheral blood and bone marrow should be evaluated at each AML disease assessment. The type of testing and the conditions of testing at the End-of-Therapy were also clarified for peripheral blood, bone marrow, and radiological assessments of AML disease status.
- It was clarified that hospital admissions or prolongations of hospitalization for administration of concomitant or subsequent therapy for the cancer would not be considered serious.

14.11.2 Specific Changes

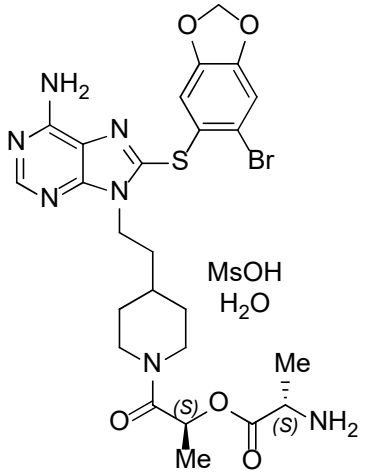
In preparing Amended Version 7 of the protocol document, the following specific changes were made. Explanations of the changes are provided in italics as "***Changes/Rationale***". Inserted text is indicated by double-underlining. Deleted text is indicated by ~~strikeout~~. Revisions to the synopsis are not described because analogous changes were made in the body of the protocol.. Changes to the protocol versions and dates, modifications to the list of abbreviations and definitions of terms, routine bibliographic reference updates, or minor typographical or syntax corrections are not indicated. References to the former company name (LAM Therapeutics, Inc.) were updated to the current company name (AI Therapeutics, Inc.) without indicating the specific locations of these changes.

Changes/Rationale: The introduction to the protocol was updated to document the expected LAM-003→LAM-003A conversion ratio and summarize the available clinical experience with LAM-003 from this clinical trial; these changes were made to support the plan to evaluate additional LAM-003 dose levels.

1 INTRODUCTION, 1.4 LAM-003/LAM-003A, 1.4.2. Chemistry

LAM-003 has the chemical name of [(1S)-2-[4-[2-[6-amino-8-[(6-bromo-1,3-benzodioxol-5-yl)sulfanyl]purin-9-yl]ethyl]-1-piperidyl]-1-methyl-2-oxo-ethyl] (2S)-2-aminopropanoate mono-mesylate, mono-hydrate]. The structure is shown in Figure 1.

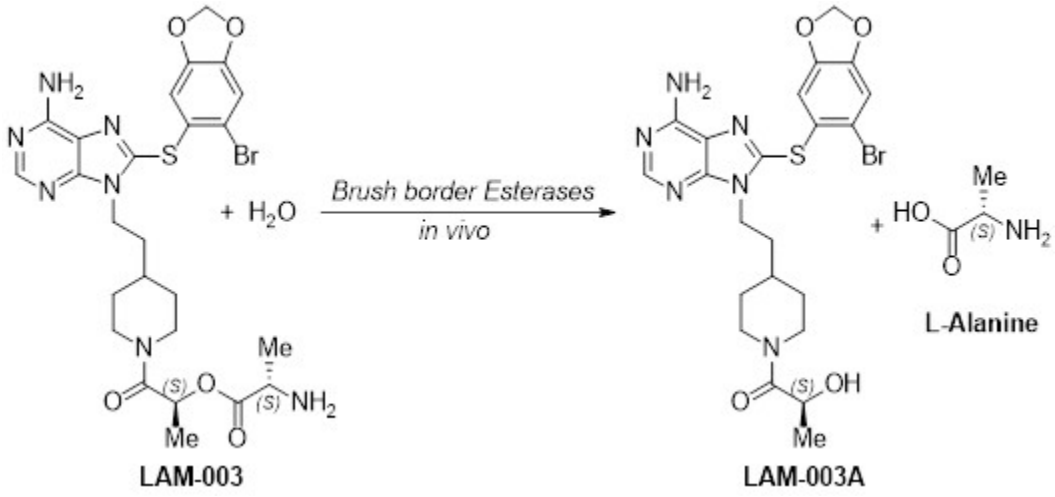
Figure 1. LAM-003 Structure



The molecular formula is $C_{25}H_{30}BrN_7O_5S \bullet CH_4O_3S \bullet H_2O$ and the molecular weight is 734.64 g/mole. LAM-003 is modestly soluble in water (350 µg/mL). The logarithm of the acid dissociation constant (pKa) is 6.91.

LAM-003 is the L-alanine prodrug of the active moiety LAM-003A. LAM-003 is converted by esterases to LAM-003A. This conversion occurs in vitro in culture media and in vivo at the brush border of the intestine as shown in Figure 2. Based on a LAM-003A molecular weight of 549.44, and assuming complete conversion, administration of LAM-003 is expected to result in delivery of ~75% of the LAM-003A that would occur with direct administration of LAM-003A.

Figure 2: In Vivo Conversion of LAM-003 to LAM-003A and L-Alanine



1 INTRODUCTION, 1.4 LAM-003/LAM-003A, 1.4.4 Clinical Experience

1.4.4.1 Phase 1 Study of LAM-003A

~~No studies of LAM-003 have been conducted.~~ A Phase 1, multicenter (3 centers), open-label, dose-ranging, multiple-dose study was conducted by the previous sponsor (Myrexis) to evaluate the safety and pharmacokinetics and to determine the maximum tolerated dose (MTD) of LAM-003A in patients with advanced solid tumors.

Twenty-six subjects (13 males and 13 females) of median age 63.5 years (range: 45 to 85 years) with diverse types of tumor histologies (ie, cancers of the breast, colon, lung, prostate, kidney, salivary gland; melanoma, mesothelioma, sarcoma; unknown primary) were enrolled to receive repeated 21- to 28-day cycles of LAM-003A self-administered orally on a QD or twice-per-day (BID) schedule. Dosing regimens included 50 mg/m^2 QD (n=1), 100 mg/m^2 QD (n=1), 165 mg/m^2 QD (n=1), 245 mg/m^2 QD (n=6), 340 mg/m^2 QD (n=2), 340 mg/m^2 BID (n=6), 240 mg BID (n=4), and 320 mg BID (n=5). Subjects received a mean of 1.7 cycles of therapy (range, 0 to 13 cycles).

Based on pre-established definitions of dose-limiting toxicity (DLT), an MTD was not determined. However, the drug was not well tolerated at total doses of >600 mg per day due to Grade 1-3 gastrointestinal adverse events (AEs) of nausea, vomiting, abdominal pain, diarrhea, and/or enteritis in 10/10 subjects.

Cardiovascular-related AEs were considered possibly related to the study drug in 3 subjects; these events included Grade 1 sinus tachycardia in 2 subjects in the 640-mg dose group and Grade 3 supraventricular tachycardia in 1 subject in the 245-mg/m^2 dose group. Electrocardiograms that were monitored on Days 1 and 21 for 8 to 12 hours indicated corrected QT intervals by the Fridericia correction method (QTcF) of >450 msec and ≤480 msec (Grade 1) in 4 of the 26 subjects. A prolonged QTcF interval (>500 msec) was noted in 1 subject; however, this subject had a pacemaker and the finding was not considered clinically relevant.

At doses of >600 mg per day, Grade 1-2 recoverable vision changes of light/dark adaptation difficulty, dark/dimmed vision, white ocular crescents, and/or floaters were observed in

3/10 subjects (consistent with known class effects for HSP90 inhibitors [Pacey 2011, Rajan 2011, Sessa 2013, Infante 2014, Bendell 2015, Shapiro 2015, Bendell 2016, Kong 2016]).

Other notable potentially drug-related AEs included renal failure (1 subject) and respiratory failure (1 subject).

Pharmacokinetic findings indicated median T_{max} values in the range of 1 to 3 hours. C_{max} and AUC increased in a nearly dose-proportional manner across the dose levels. Exposures were generally 1- to 2-fold greater on Day 21 than on Day 1, indicating minimal to modest drug accumulation. The average t½ based on all cohorts after repeated dosing was 11.2 hours, supporting QD or BID dosing.

1.4.4.1 Phase 1 Study of LAM-003 (Current Study)

This ongoing Phase 1 multicenter, open-label, 3+3 dose-escalation study is being conducted by AI Therapeutics to evaluate the safety and pharmacokinetics and to determine the MTD of LAM-003 in patients with previously treated, relapsed or refractory AML. As of a cut-off date of 10 Jun 2019, 9 subjects (6 males and 3 females) ranging in age from 26 to 82 years had received LAM-003 self-administered orally on a QD schedule. Dosing regimens included 200 mg QD (total n=6, DLT evaluable n=3) and 300 mg QD (total n=3, DLT evaluable n=3). Durations of LAM-003 administration at 200 mg QD were 2, 9, 12, 28, 56, and 57 days. Durations of LAM-003 administration at 300 mg QD were 21, 28, and 36 days. Reasons for discontinuation were progressive disease or lack of sufficient treatment response (n=8) or intercurrent illness due to AML complications (n=1).

AEs appeared to be primarily related to AML, comorbid medical conditions, intercurrent illness or concomitant medications. Obvious LAM-003-related toxicities were not evident and no DLTs occurred. Laboratory or ECG abnormalities clearly attributable to the study drug were not observed. No drug-related ophthalmological findings were described.

Pharmacokinetic data were available from subjects at LAM-003 dose levels of 200 mg QD (Day 1, n=4; Day 8, n=3) and 300 mg QD (Day 1, n=3; Day 8, n=3). As expected, exposure to the prodrug (LAM-003) in the systemic circulation was below the lower limit of quantitation of the assay (<1.0 ng/mL). LAM-003A exposures in the plasma was observed in all subjects. Increases in LAM-003A exposures were generally proportional to increases in LAM-003 dose. It appeared that LAM-003A steady state was achieved between Day 1 and Day 8; LAM-003A concentrations at 24 hours following the first dose on Day 1 were comparable to trough levels on Day 8 and LAM-003A AUC values were similar on Days 1 and 8. The pharmacokinetic profile of LAM-003A following LAM-003 administration was consistent with that observed with LAM-003A administration in the prior Phase 1 experience in patients with solid tumors.

Changes/Rationale: Information regarding the number of subjects to be accrued was modified consistent with other changes to the protocol.

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.1 Planned Number of Subjects

The total number of subjects will depend upon the numbers of subjects accrued to each dose level and the number of dose levels evaluated. If 6 subjects are enrolled at all ~~3~~ 5 planned starting dose levels and 6 additional subjects are enrolled at the MTD or RDR, as many as ~~24~~ 36 subjects could be enrolled. If an additional dose level or an additional schedule (eg, BID)

administration is explored in 6 subjects per cohort, as many as 12 additional subjects could be enrolled, bringing the potential sample size to ~~36~~ 48 subjects. To allow for the possibility that some subjects may not be fully evaluable, up to ~~48~~ 60 subjects may be enrolled.

Changes/Rationale: During accrual to the study, investigational sites had occasionally noted spuriously high values for cardiac QT interval when correcting with the Bazett formula (QTcB). These findings are consistent with published literature indicating that the QTcB tends to overestimate the QT interval and that correction using the Fridericia formula (QTcF) provides more accurate data in adults. In addition, the FDA had indicated that the QTcF alone is acceptable in analyzing QT data from clinical trials in adults. Based on these observations and considerations, it was elected to use only the QTcF value for purposes of establishing eligibility, determining DLT, assessing potential critical QT alerts, and statistical analyses.

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5. Subject Selection Criteria, 5.5.2 Exclusion Criteria, Exclusion Criterion 6

6. Significant screening ECG abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, left bundle-branch block, 2nd-degree atrioventricular (AV) block type II, 3rd-degree AV block, Grade ≥2 bradycardia, or corrected QT (QTc by Fridericia ~~or Bazett~~ method) >480 msec (Grade >1).

11 STATISTICAL CONSIDERATIONS, 11.2 Analysis Plan, 11.2.3 Safety, 11.2.3.4 Electrocardiography

The overall quantitative and qualitative ECG assessment of heart rate, cardiac intervals, wave form abnormalities, and ectopy will be reported as "Normal" or "Abnormal" with respect to the description of the official ECG reading provided by the CRO performing the ECG analyses. A shift table comparing the ECG assessment over the on-study period (ever abnormal) to baseline will be presented with the types of abnormalities tabulated.

Quantitative ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTc interval) at each time recorded as well as the change from screening will be summarized with descriptive statistics. The QT interval will be corrected by the Fridericia method for purposes of analysis. The following formula will be employed for correction: ~~The QT interval will be corrected by both the Bazett and Fridericia method as follows:~~

- ~~Bazett: $QTcB = QT/(RR)^{1/2}$~~
- Fridericia: $QTcF$ in msec $= QT/(RR/1000)^{1/3}$

The QTc data obtained by using the ~~Bazett and~~ Fridericia correction will be categorized separately into the following classifications and summarized by time point:

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

The change of the QTc values obtained by using the ~~Bazett's and~~ Fridericia~~'s~~ correction will also be categorized separately as follows:

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

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

In post-marketing surveillance, rare instances of cardiac QT prolongation and ventricular dysrhythmias had been observed in patients taking fluconazole. For this reason, fluconazole was listed in Appendix 14.5 as a drug having a known association with QT prolongation and thus its use was proscribed per protocol. However, as documented in fluconazole product labeling, most of the case reports of increases in QT interval were limited to patients with confounding disease, drug, or electrolyte risk factors. Accordingly, the protocol was updated to indicate that concomitant use of fluconazole prophylaxis/therapy would be permitted in subjects enrolled to the study. Further, it was indicated that the medical monitor could sanction use of certain concomitant drugs if the risk of QT prolongation in a specific study subject was likely to be negligible.

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5. Subject Selection Criteria, 5.5.2 Exclusion Criteria, Exclusion Criterion 17

17. Use within 7 days prior to the start of study therapy of a drug known to prolong the QT interval (see Appendix 14.5). ***Note: For subjects requiring antifungal prophylaxis/therapy, oral fluconazole is permitted given that the risk of QT prolongation is considered low (as documented in product labeling).***

6 **STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.3 Supportive Care, 6.3.10 Drugs Known to Prolong the QT Interval**

Available nonclinical and clinical data do not suggest a high risk that LAM-003 will alter the QT interval. However, data are limited and, as a precaution, the clinical potential of LAM-003 to prolong the QT interval will be assessed in this study. Accordingly, co-administration of LAM-003 and known QT-prolonging drugs is to be minimized during Cycle 1 because use of such drugs might confound interpretation of QT data from the trial.

Based on these considerations, protocol candidates who require therapy with drugs known to prolong the QT interval (as listed in Appendix 14.5) should not be enrolled into the study. If medically justified, protocol candidates may be enrolled if such drugs are unlikely to result in QT prolongation in the specific study subject (as judged by the medical monitor), can be discontinued, or alternative drugs that do not affect QT can be substituted >7 days before the first dose of LAM-003.

After the subject is enrolled to the protocol and has been monitored for 24 hours after receiving the first dose of LAM-003, there is no specific restriction on use of drugs (eg, antiemetics) that might prolong QT interval; however, use of such drugs should be minimized.

Changes/Rationale: The exclusion criterion relating to participation in another therapeutic or imaging clinical trial was clarified.

5 RECRUITMENT AND SELECTION OF STUDY SUBJECTS, 5.5. Subject Selection Criteria, 5.5.2 Exclusion Criteria, Exclusion Criterion 18

18. Concurrent participation in another therapeutic or imaging clinical trial. ***Note: Subjects are not precluded from undergoing evaluations involving observation, noninvasive diagnostic procedures or sampling, or questionnaires as follow-up to a prior study or as components of a concurrent noninterventional study.***

Changes/Rationale: The need for documentation of the timing of LAM-003 administration in conjunction with frequent pharmacokinetic assessments was emphasized

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.2 LAM-003 Administration

In each 28-day cycle, subjects are to self-administer LAM-003 starting on Day 1 and then continuously thereafter (28 total doses/cycle). Subjects should take the study drug at approximately the same time each day, ideally at ~24-hour intervals (eg, ~8AM every day) for the planned QD schedule or at 12-hour intervals (eg, ~8AM and ~8PM every day) if a BID schedule is evaluated. In conjunction with frequent pharmacokinetic assessments on C1D1, C1D2, and C1D8, subjects should take the drug at the study center under the supervision of study personnel and the timing of LAM-003 administration must be documented in the clinic notes and/or in the subject diary. On C1D2, C1D3, C1D4, and C1D5, LAM-003 is to be administered in the study center and only after the serum chemistry results from that day have been evaluated to exclude Grade 4 TLS or Grade 3 TLS associated with Grade ≥2 renal dysfunction or other Grade ≥2 end-organ injury. While variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible.

Changes/Rationale: The definition of an overdose was changed to accommodate changes in the dose range of LAM-003 being explored in the study.

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.1 LAM-003, 6.1.8 Overdose Precautions

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the overdose limit. In the case of a discrepancy in drug accountability, an overdose will be established only when it is clear that the subject has received an excess dose or the investigator has reason to suspect that the subject has received an excess dose.

There are limited data on the effects of LAM-003 overdose. LAM-003A doses as high as 320 mg BID (640 mg QD) were achieved in a prior Phase 1 study.

For this protocol, an overdose of LAM-003 is defined as administration of a daily dose ~~≥600 mg~~≥50 mg above the prescribed dose. In a subject who experiences an overdose, consideration should be given as to whether LAM-003 administration should be temporarily interrupted. If the overdose is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and safety laboratory parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management should be

instituted to mitigate adverse effects. The subject should remain under observation until adverse effects have recovered to baseline. There is no specific antidote for LAM-003.

The medical monitor should be contacted if a study drug overdose occurs. The occurrence of an overdose does not preclude further protocol therapy if the subject appears to be safely benefiting from treatment and the circumstances that led to the initial overdose are unlikely to recur.

Changes/Rationale: Prior Phase 1 clinical dose ranging with the active LAM-003 metabolite, LAM-003A, established an MTD in the range of 480 mg/day to 600 mg/day. LAM-003A dosing was not limited by high-grade DLTs but by reversible low-grade nausea vomiting at doses >600 mg/day. In the current LAM-003 study, it was considered possible that administration of LAM-003 as a prodrug for LAM-003A might result in lower effective drug exposure at higher dose levels than was previously observed when administering the metabolite directly. LAM-003 administration in this study at dose levels of 200 mg QD and 300 mg QD demonstrated no discernable toxicity, justifying an increment in dose level to a planned 450 mg QD. Based on these considerations and the evolving LAM-003 safety profile, it was anticipated that exploration of higher LAM-003 dose levels might be warranted. Accordingly, it was elected to add LAM-003 dose levels of 600 mg (1.33-fold increment) and 750 mg QD (1.25-fold increment) to the dose escalation-scheme. Actual dose escalation continued using the existing 3+3 paradigm, DLT definitions, and safety monitoring; thus, all existing safety protections remained in place.

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.4 Starting Dose Levels and Dose Escalation, Table 1 (LAM-003 Starting Dose Levels)

Cohorts of 3 to 6 subjects will be 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 will be 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 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

Abbreviations: QD=once per day

Changes/Rationale: Exploration of BID dosing was permitted per the existing protocol with the expectation that study subjects would receive divided doses that were half of the total daily dose in multiple of 50 mg (considering the 50-mg LAM-003 tablet size). The introduction of a potential total dose of 750 mg/day could result in unequal morning and evening dosing on a BID schedule. Thus, a provision for rounding up or down was introduced into the protocol (eg, 750 mg/day could be evaluated as 350 mg BID or 400 mg BID depending upon the emerging safety and pharmacokinetic profile of the drug).

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.4 Starting Dose Levels and Dose Escalation, Sub-bullet

The following dose-escalation rules will be employed, considering DLTs observed in Cycle 1 of therapy:

- Each dose level cohort will initially enroll 3 subjects.
- If 0 of the first 3 subjects has a DLT, the next cohort of 3 subjects will be treated at the next higher dose level.
- If 1 of the first 3 subjects in a cohort experiences a DLT, an additional 3 subjects will be treated at that same dose level. If 0 of the additional 3 subjects experience a DLT, the next cohort of 3 subjects will be treated at the next higher dose level.
- If ≥2 of 3 or ≥2 of 6 subjects experience a DLT, the MTD will have been exceeded and 3 more subjects will be treated at the next lower dose level (if only 3 subjects were previously treated at that prior dose level). If 6 subjects were previously treated at the prior dose level, that prior dose level will provisionally be considered the MTD.
- An additional 6 subjects (up to 12 total) may be enrolled at the MTD or RDR.
- With the concurrence of the SRC, additional subjects (up to 12 subjects per dose level) may be accrued at dose levels at or below the MTD to refine the estimation of the RDR and further define the pharmacology of LAM-003. Such accrual may occur:
    - At Dose Level -1 or -2 (100 or 50 mg of LAM-003, respectively).
    - At an initially planned dose level (as indicated in Table 1) or at a dose level that lies between the initially planned dose levels.
    - Using an alternative schedule (eg, BID) with a total daily dose that does not exceed the total daily MTD (rounded up or down to the nearest even multiple of 50 mg).

Changes/Rationale: The requirement for a minimum period of 4 weeks of observation was made approximate to allow some latitude in the DLT observation period consistent with the allowed visit window (±3 days).

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.4 Starting Dose Levels and Dose Escalation, Bullet

The following additional procedures will be followed during the dose escalation:

- The first subject to be treated at Dose Level 1 will be observed for ≥1 week after initiation of LAM-003 before any subsequent subjects are treated at the same dose level.
- Each group of 3 subjects within a cohort must receive ≥75% (21/28 doses for a QD schedule or 42/56 doses for a BID schedule) of planned Cycle 1 LAM-003 doses per subject and must be observed for a minimum period of ≧4 weeks without DLT before subsequent subjects are enrolled at the next higher dose level. Any subject without DLT who does not complete these requirements may be replaced.
- Escalation to the next dose level can only occur upon review of the available safety data from all ongoing and previous subjects and with the concurrence of the SRC.
- Intrasubject dose escalation above the initially assigned dose level will be not be permitted except as defined in Section 6.2.7 below.
- Accrual of additional subjects to a treatment cohort may be considered by the SRC with the concurrence of the study sponsor.

Changes/Rationale: Changes were incorporated into dose modification recommendations to maximize the potential for clinical benefit in individual subjects who proved to be tolerating therapy at a lower dose level and might safely benefit from a dose-escalation. In making these changes, safeguards were maintained: subjects must have tolerated therapy with no toxicities of Grade ≥2, only successive dose-level adjustments were permitted, the dose could not have exceeded an established MTD, the potential for additional monitoring was incorporated, and both the investigator and the medical monitor must have agreed that the dose escalation was medically appropriate.

6 STUDY DRUG INFORMATION, ADMINISTRATION, AND SUPPORT, 6.2 Study Drug Administration, 6.2.7 Dose Modification Recommendations, 4th Paragraph

Individual subjects who initiated treatment at a dose level below the dose currently under study or the established MTD (if lower) may have the LAM-003 dose escalated to the next higher dose level after ≥2 cycles of therapy if both the principal investigator and the medical monitor agree that the subject is tolerating the current dose level with no toxicities of Grade ≥2 and that a dose escalation is medically warranted (~~ie~~ eg, for a subject with a PR). In such subjects, successive adjustments to progressively higher dose levels can be made at intervals of ≥4 weeks with the caveat that the escalated dose ~~level~~ cannot exceed the dose level currently under study or the established MTD (if lower). If considered necessary by the medical monitor, certain safety and other studies (eg, serum chemistry, hematology, ECG, pharmacokinetic, and pharmacodynamic evaluations) may be repeated at the higher dose level per the Cycle 1 schedule for these tests.

Changes/Rationale: It was clarified that ophthalmological testing could be performed by ophthalmologists or optometrists but also by other specialists with the relevant expertise (eg, a neurologist for ERG testing).

It was also noted that the medical monitor could approve omission of an End-of-Therapy ophthalmological evaluation; this change was implemented to provide some flexibility to deal with extenuating circumstance (eg, avoid repeat testing in a subject who had recently undergone ophthalmological testing or was too ill due to AML to be transported to the ophthalmology clinic).

7 STUDY ACTIVITIES AND ASSESSMENTS, Table 3 (Schedule of Activities), Footnote l.

l.	Ophthalmology evaluations (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography) should be performed by an ophthalmologist, ~~or~~ optometrist, or other qualified specialist during Screening, within 14 days before C2D1 (4-week interval), within 14 days before C4D1 (8-week interval), and then within 14 days before C7D1, C10D1, C13D1, C16D1, etc (12-week intervals), and at End-of-Therapy. An End-of-Therapy ophthalmologic evaluation may be omitted with the approval of the medical monitor.

9 LABORATORY AND OTHER ASSESSMENTS, 9.1 Methods and Analytes, Paragraph 9.

Ophthalmological examinations should be performed by a consulting ophthalmologist, ~~or~~ optometrist, or other qualified specialist with the necessary facilities and equipment to perform appropriate testing (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography); interpretations of ophthalmological findings will be provided by a consulting ~~ophthalmologist~~ specialist.

9 Laboratory and Other Assessments, 9.1 Methods and Analytes, Table 8 (Laboratory and Other Parameters to Be Assessed), Body of Table.

Ophthalmology examination	• Examination by an ophthalmologist, ~~or~~ optometrist, or other qualified specialist (including visual symptom assessment, visual acuity testing, electroretinography, tonometry, slit lamp examination, and electrical coherence tomography))

Changes/Rationale: It was clarified that both peripheral blood and bone marrow should be evaluated at each AML disease assessment. The type of testing and the conditions of testing at the End-of-Therapy were also clarified for peripheral blood, bone marrow, and radiological assessments of AML disease status.

7 STUDY ACTIVITIES AND ASSESSMENTS, Table 3 (Schedule of Activities), Footnotes ff and gg.

ff.	Blood for peripheral blood AML blast count evaluation and bone marrow aspiration/biopsy will be performed during Screening (unless the requirement for screening bone marrow aspirate/biopsy is waived by the medical monitor because sufficient bone marrow material is available for response determination). Post-baseline, a peripheral blood AML blast count evaluation and a bone marrow aspirate/biopsy is required within 14 days before C3D1, C5D1, C7D1 (8-week intervals), and then within 14 days before C10D1, C13D1, C16D1, etc (12-week intervals). An End-of-Therapy peripheral blood AML blast count evaluation and a bone marrow aspirate/biopsy should be performed unless the subject already has hematological or radiographic confirmation of TF or DRP ≤8 weeks before permanent study drug discontinuation or the medical monitor approves omission of such End-of-Therapy testing. At all AML evaluations, the extent of involvement with AML in peripheral blood and bone marrow, the presence of Auer rods, and bone marrow cellularity will be assessed. Bone aspirate aliquots obtained at Screening and within 14 days before C3D1 may also be evaluated for FLT3/HSP protein and gene expression, PD-L1, and AML mutations.
gg.	Radiology examination is required in subjects with extramedullary disease that is radiographically assessable. FDG-PET/CT is the preferred method of evaluation but other methods (diagnostic CT, MRI) may be used if appropriate for the type of lesion. The baseline evaluation should occur within 28 days before C1D1. Post-baseline evaluations should be performed within 7 days before C3D1, C5D1, C7D1 (8-week intervals), and then within 7 days before C10D1, C13D1, C16D1, etc (12-week intervals). An End-of-Therapy radiology assessment should be performed unless a subject with extramedullary disease already has hematological or radiographic confirmation of TF or DRP ≤8 weeks before permanent study drug discontinuation or the medical monitor approves omission of such End-of-Therapy testing.

10 EFFICACY ASSESSMENTS, 10.3 Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within the specified screening period. On-study tumor assessments should be performed as indicated in Section 7. An end-of-therapy tumor assessment should be performed unless the subject already has confirmation of TF or DRP ≤8 weeks prior to study drug discontinuation or the medical monitor has waived the requirement. If a subject permanently discontinues treatment prior to objective documentation of AML progression, investigators should continue further follow-up of tumor status with assessments at ~8- to 12-week intervals until disease progression is documented or until the initiation of a new post-study therapy for the subject's AML.

Changes/Rationale: It was clarified that hospital admissions or prolongations of hospitalization for administration of concomitant or subsequent therapy for the cancer would not be considered serious.

8. SAFETY ASSESSMENTS, 8.1 Definitions, 8.1.2 Serious Adverse Events, Bullet

- In-patient hospitalization or prolongation of existing hospitalization. Of note, an untoward medical occurrence that occurs during hospitalization is an AE but a complication that prolongs hospitalization is an SAE. In-subject hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions or prolongations of hospitalization for administration of the study drug or procedures required by the study protocol, diagnostic observations or procedures, administration of concomitant or subsequent therapy for the cancer, logistical issues (eg, lengthy travel), or the convenience of the subject or clinical personnel are not considered serious.

14.12 Summary of Changes to Protocol – Amended Version 8

14.12.1 Overview of Changes

The modifications from Version 7 to Version 8 of the protocol are summarized as follows:

- The contact information for the clinical operations manager for the study was updated.
- The intrapatient dose-escalation provisions and duration of study drug administration instructions were altered to maximize the potential for clinical benefit in individual subjects who proved to be tolerating therapy at a lower dose level and might safely benefit from a dose-escalation.

14.12.2 Specific Changes

In preparing Amended Version 8 of the protocol document, the following specific changes were made. Explanations of the changes are provided in italics as "***Changes/Rationale***". Inserted text is indicated by double-underlining. Deleted text is indicated by ~~strikeout~~. Revisions to the synopsis are not described because these are described in the body of the protocol. Changes to the protocol versions and dates, modifications to the list of abbreviations and definitions of terms, routine bibliographic reference updates, or minor typographical or syntax corrections are not indicated.

Changes/Rationale: Due to changes in study personnel, the contact information for the clinical operations manager for the study was updated.

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Changes/Rationale: The intrapatient dose-escalation provisions and duration of study drug administration instructions were altered to maximize the potential for clinical benefit in individual subjects who proved to be tolerating therapy at a lower dose level and might safely benefit from a dose-escalation. In making these changes, safeguards were maintained: subjects must have tolerated therapy with no toxicities of Grade ≥2, only successive dose-level adjustments were permitted, the dose was limited to 750 mg QD (an exposure level for which there is experience in a prior Phase 1 study of LAM-003A in subjects with solid tumors), both the investigator and the medical monitor must have agreed that the dose escalation was medically appropriate, and additional safety and other monitoring was mandated.

6.2.4 Starting Dose Levels and Dose Escalation, Bullet Point

- Intrasubject dose escalation above the initially assigned dose level will be permitted ~~will not be permitted~~ except as defined in Section 6.2.7 below.

Section 6.2.7 Dose Modification Recommendations, Paragraph 4

Individual subjects may have the LAM-003 dose escalated to the next higher dose level after ≥1 cycle of therapy if both the principal investigator and the medical monitor agree that the subject is tolerating the current dose level with no toxicities of Grade ≥2 and that a dose escalation is medically warranted to try to obtain better disease control (eg, for a subject who has not shown an improvement in AML disease burden by the end of the cycle). In such subjects, successive adjustments to progressively higher dose levels can be made at intervals of >4 weeks with the caveat that the escalated dose cannot exceed 750 mg QD (highest plan dose level) or the established MTD (if lower). As directed by the medical monitor, certain safety and other studies (eg, serum chemistry, hematology, ECG, ophthalmology, pharmacokinetic, and pharmacodynamic evaluations) may be repeated at the higher dose level per the Cycle 1 schedule for these tests.

~~Individual subjects who initiate treatment at a dose level below the dose currently under study or the established MTD (if lower) may have the LAM-003 dose escalated to the next higher dose level after ≥2 cycles of therapy if both the principal investigator and the medical monitor agree that the subject is tolerating the current dose level with no toxicities of Grade ≥2 and that a dose escalation is medically warranted (eg, for a subject with a PR). In such subjects, successive adjustments to progressively higher dose levels can be made at intervals of ≥4 weeks with the caveat that the escalated dose cannot exceed the dose level currently under study or the established MTD (if lower). If considered necessary by the medical monitor, certain safety and other studies (eg, serum chemistry, hematology, ECG, pharmacokinetic, and pharmacodynamic evaluations) may be repeated at the higher dose level per the Cycle 1 schedule for these tests.~~

6.2.5 Duration of Study Drug Administration and Study Participation

Subjects may receive LAM-003 therapy indefinitely. However, the occurrence of any of the following events requires treatment discontinuation:

- Subject request to withdraw from study treatment
- Documented objective evidence of treatment failure or of AML relapse or progression (see Section 10.4.5 and Section 10.4.6 for definitions) while receiving study treatment at the highest individually tolerated dose level
- For a subject in PR, continued red blood cell transfusion dependence at Week 20

- Intolerable toxicity despite appropriate supportive care and/or dose modification
- Failure to recover to Grade ≤1 or baseline within 2 weeks from the last dose of LAM-003 following interruption for a TEAE that is not primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant medication
- The development of intercurrent illness or other substantial change in the subject's condition or circumstances that would place the subject at unacceptable risk as determined by the study investigator in consultation with the medical monitor
- Initiation of treatment for the subject's cancer with an off-study therapeutic regimen
- Pregnancy or breastfeeding
- Substantial noncompliance with study drug administration, study procedures, or study requirements in circumstances that increase risk or substantially compromise the interpretation of study results
- Discontinuation of the study by the study center, the study sponsor, relevant regulatory agencies, or the IRB/IEC

Unless they withdraw consent for further follow-up, subjects who discontinue study therapy will continue on study for acquisition of safety information through ≥30 days after the last dose of study treatment, and for further collection of information regarding additional therapies for their cancer and OS.