MD Anderson IND Sponsor Cover Sheet	
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Protocol Title	**Phase 1 Study of IACS-010759 in Subjects with Relapsed or Refractory AML**
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Protocol PI	Marina Konopleva, M.D.
Department	Leukemia
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Phase 1 Study of IACS-010759 in Subjects with relapsed or refractory AML

Study Synopsis and Objectives

This is an open label Phase 1 study of IACS-10579 utilizing a 3+3 dose-escalation phase followed by an expansion phase in subjects with relapsed or refractory AML and no available treatment options with known benefit.

In cohorts 1 and 2, in the first cycle, IACS-010759 will be administered on Day 1 followed by continuous dosing starting on day 8 through day 28; cycles 2 and beyond will be continuous daily dosing. Based on PK analysis and modeling of preliminary data from cohorts 1 and 2, the study design has been amended. In cohort 3 and subsequent cohorts, in the first cycle, IACS-010759 will be administered daily for up to 7 days during an initial Induction Phase (Day 1-7) followed the Maintenance Phase (Day 8-21), which will use a lower dose to maintain steady state drug levels. For cohort 3, the maintenance dose will be administered once weekly on Day 8 and Day 15 of the 21-day cycle in cycle 1; in subsequent cycles, doses will be administered on Days 1, 8 and 15 of each cycle, unless alternate schedules are recommended by the SMC. In subsequent cohorts, the induction and maintenance doses and/or the dosing interval during the maintenance phase may be further modified by the SMC based on safety, PK and PD data observed. Dosing will continue until confirmed progressive disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment prematurely at the dose levels given below:

Original Dose Escalation Regimen, Cohorts 1 and 2:

PHASE	COHORT	NO OF SUBJECTS	IACS-010759 DOSE LEVEL (DAILY EXCEPT CYCLE 1, DAY 2-7) *
Dose-escalation	Cohort 1	3-6	0.5 mg
	Cohort 2	3-6	1 mg

*Intermediate doses of IACS-010759, not to exceed 8 mg, not listed above may also be pursued with SMC approval depending on the safety, PK and PD data observed.

Revised Dose Escalation Regimen for Cohorts 3-6 and Expansion Regimen for Cohort 7:

PHASE	COHORT	NO OF SUBJECTS	INDUCTION DOSE* (FREQUENCY#)	MAINTENANCE DOSE* (FREQUENCY)
Dose-escalation	Cohort 3	3-6	2 mg (daily, Cycle 1 Day 1-7)	0.5 mg (once per week)
	Cohort 4**	3-6	2.5 mg (daily, Cycle 1 Day 1-7)	1.0 mg (three times per week)
	Cohort 5	3-6	2.5 mg (daily, Cycle 1 Day 1-5)	1.5 mg (three times per week)
	Cohort 6	3-6	3 mg (daily, Cycle 1 Day 1-5)	2 mg (three times per week)
Expansion	Cohort 7	12	RP2D	RP2D

*Intermediate induction or maintenance doses of IACS-010759, not to exceed 6 mg, and #alternative duration of induction doses or other maintenance schedules not listed above may also be pursued with SMC approval depending on the safety, PK and PD data observed.

**Following their review of Cohort 3, the SMC recommended implementation of the following dose schedule for subjects who enroll in Cohort 4 of the study:

Induction dose: 2.5 mg, administered daily, Cycle 1 Day 1 through Day 7

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Maintenance dose: 1 mg, administered 3x/week (for a total weekly dose of 3 mg) with the first maintenance dose starting on Cycle 1 Day 8 Subjects in the expansion phase will be treated at the recommended phase 2 dose (RP2D) identified in the dose-escalation phase, using the induction + maintenance regimen. Up to 48 subjects will be enrolled in the study: a maximum of 36 subjects in the dose-escalation and a maximum of 18 subjects in the expansion phase (12 additional subjects and the 6 subjects from the dose-escalation phase at the cohort of the highest dose level shown to be well tolerated or the recommended phase 2 dose). The primary objective is to determine safety and tolerability of IACS-010759, the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). The secondary objectives are IACS-010759 pharmacokinetics, food effect, and preliminary clinical efficacy (overall response rates, duration of response, progression-free survival, overall survival). The exploratory objective is to evaluate pharmacodynamic (PD) and exploratory biomarkers of activity of IACS-010759.

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1 Protocol Amendments

Section	Text	Amendments	Rationale for Change
Amendment #10 (dated 21 January 2019)			
Synopsis, 3.1, 4.1.6, 4.1.7, 4.2	Revised	Revised the induction phase duration from 7 days to up to 7 days	SMC recommendation at end of cohort 4 to reduce the daily induction phase dosing from 7 days to 5 days starting in cohort 5
Synopsis, 4.1.6	Revised	Modified the cohort 5 dosing regimen to 2.5 mg induction (daily, Cycle 1 Day 1 through Day 5) and 1.5 mg maintenance (3 times per week starting on Cycle 1 Day 8)	SMC recommendation
Synopsis, 4.1.6	Revised	Modified the cohort 6 dosing regimen to 3 mg induction (daily, Cycle 1 Day 1 through Day 5) and 2 mg maintenance (3 times per week starting on Cycle 1 Day 8)	Original dose regimen for cohort 6 not likely to be tolerated based on available interim data
4.2	Revised	Changed Cycle 1 Day 7 visit to Cycle 1 Day 5 visit starting with subjects enrolled in cohort 5	Collection of PK data based on revised dosing regimen
4.2	Added	Added PK assessment 24 hours post study drug administration on Cycle 1 Day 5 starting with subjects enrolled in cohort 5	Revised dosing regimen
4.2	Removed	Removed days allowable for Cycle 1 Day 5 and Cycle 1 Day 8	Consistency of PK data based on revised dosing regimen
Throughout	Clarification	Corrected typographical errors	Consistency and readability of protocol
Amendment #9 (dated 13 September 2018)			
4.2	Added	Added baseline dilated eye exam with fundus photos and neurology & exam (prior to Cycle 1 Day 1 study drug administration)	SMC recommendation
5.2	Added	Updated eligibility to exclude patients with ≥ grade 1 peripheral neuropathy	SMC recommendation
Amendment #8 (dated 06 June 2018)			
4.1.3, 5.1	Removed	Removed eligibility requirement that subjects must have failed to achieve CR to standard induction therapy	Increased flexibility at site based on available subject safety information from this study and ongoing solid tumor study (IACS2016-002)
Amendment #7 (dated 27 February 2018)			

Section	Text	Amendments	Rationale for Change
Synopsis, 4.1.6	Added	Added dosing schedule to be implemented in Cohort 4, based on SMC recommendation	SMC Recommendation
Synopsis, 3.1, 4.1.6	Clarification	Clarified that modified induction or maintenance doses or alternative maintenance schedules may be pursued with SMC approval depending on the safety, PK and PD data observed	Informational
6.1	Clarification	Corrected typographical error	Informational
Amendment #6 (dated 04 January 2018)			
4.2	Revised	Revised days allowable for Cycle 1 Day 17 and Cycle 2 Day 16 from ±1 day to ±2 days (Cohorts 3-7)	Increased flexibility at site
4.2	Revised	Revised days allowable for Cycle 1 Day 21 to allow +2 days (Cohorts 3-7)	Increased flexibility at site
4.2	Revised	Revised definition of "pre-dose" from within 3 hours of dosing to same calendar day of dosing (Cohorts 3-7)	Increased flexibility at site
4.2	Revised	Revised window for collection of vital signs on Cycle 1 Day and Cycle 1 Day 7 from ± 30 minutes to ± 60 minutes (Cohorts 3-7)	Increased flexibility at site
4.2	Removed	Removed vital signs and physical exam assessments on Cycle 1 Day 17 (Cohorts 3-7)	Minimize subject time at site as changes are not anticipated in specified timeframe
4.2	Deleted	Removed 4-hour post study drug administration blood hematology on Cycle 1 Days 7, 8 and 15 and removed requirement to perform pre-dose testing within 3 hours of study drug administration (Cohorts 3-7)	Minimize subject discomfort as changes are not anticipated in specified timeframe
4.2	Deleted	Removed 4-hour post study drug administration , chemistry, coagulation, lipase, amylase & urinalysis on Cycle 1 Days 7, 8, 15 and Cycle 2 Days 8 and 15 and removed requirement to perform pre-dose testing within 3 hours of study drug administration (Cohorts 3-7)	Minimize subject discomfort as changes are not anticipated in specified timeframe
5.1	Revised	Revised timeframe since relapse for subjects who previously received SCT (inclusion criterion #3)	Increased screening flexibility at site
5.1	Revised	Revised serum creatinine eligibility requirement (inclusion criterion #5)	Increased screening flexibility at site
5.1	Revised	Revised interval from time of previous investigational or non-investigational product treatment to start of IACS-010759 (inclusion criterion #9 and exclusion criterion #7)	Increased screening flexibility at site
Amendment #5 (dated 21 July 2017)			
Synopsis, 3.1, 4.1.6, 4.1.7, 7.1	Revised	Revised the dosing regimen to include an initial Induction Phase in Cycle 1 (Day 1-7) and Maintenance Phase (Day 8-21 of Cycle 1 & Days 1-21	PK analysis and modeling of data from cohorts 1 and 2

Section	Text	Amendments	Rationale for Change
		of all subsequent cycles) to start with subjects enrolled in Cohort 3	
Synopsis	Revised	Revised the authority of the SMC to approve intermediate doses to include induction or maintenance and alternative duration of induction doses or other maintenance schedules, not to exceed 6 mg (rather than 8 mg) based on the revised dosing regimen to be initiated with subjects in Cohort 3	Allows SMC to approve changes to the intermediate induction or maintenance doses, duration or schedules based on safety, PK & PD data without requiring a protocol amendment
2.2.2	Revised/ Added	Added description of results of transporter and drug-drug interaction studies	Studies complete & final data available
2.2.2, 3.1,	Added	Added description of preliminary human PK data	PK analysis and modeling of data from cohorts 1 and 2
4.1.2, 4.1.7	Revised	Revised days that PK data will be evaluated when making dose escalation decisions	Plasma concentrations will be evaluated at the end of the induction phase and again at the end of the 1st cycle, as well as at intermediate time points, based on the revised dosing regimen
4.1.7	Clarification	Provided steady state plasma levels in ng/mL	Informational
4.1.7	Revised	Revised stopping rules to assess mean plasma concentrations at the end of the induction phase of dosing (Days 7 and 8), with additional assessments at the end of each cycle	Revised dosing regimen
4.1.9	Added	If dose interruptions occur at the end of a cycle, the new cycle will start on the first day dosing resumes	Allows appropriate collection of assessments based on study drug administration
4.1.10, 4.1.11	Deleted	Removed requirement to perform arterial blood gas (ABG) testing for all abnormal venous blood pH results	Minimize subject discomfort/ will obtain for DLT confirmation, where needed, only
4.1.11	Added	Added anion gap calculation to be used for arterial blood collection	Informational
4.2	Added	Added new study flowchart based on revised dosing regimen to be implemented for subjects enrolled in Cohort 3-6 of the dose escalation phase and Cohort 7 of the dose expansion phase	PK analysis and modeling of data from cohorts 1 and 2
7.1	Revised	Revised requirement for in-hospitalization from Cycle 1 Day 1 and Day 8-14 to Cycle 1 Day 7	PK and clinical safety data from cohorts 1 and 2
8.1.3	Deleted	Removed reference to severity grading scale for AEs not defined in the NCI CTCAE Ver 4.03	Will assess all AEs according to CTCAE

Section	Text	Amendments	Rationale for Change
8.1.3	Added	Hospitalizations to observe subjects with elevated lactate who remain asymptomatic and would not otherwise require hospitalization will be not be considered a grade 3 toxicity for purposes of AE severity grading	Distinguishes between hospitalization being indicated due to severity of AE rather than for observation as required per protocol
7.2, 7.2.1	Clarification	Corrected typographical errors	Consistency and readability of protocol
Amendment #4 (dated 10 March 2017)			
Synopsis, 4.1.6	Added	Added that intermediate doses of IACS-010759, not to exceed 8 mg, may also be pursued with SMC approval, depending on the safety, PK and PD data observed	Allows intermediate doses to be evaluated during the dose escalation phase based on the observed safety, PK and PD data
4.1.7	Added	Added that a cohort may be expanded to include up to 6 subjects, in the absence of a DLT in the first 3 subjects of a cohort, with SMC approval; in that instance, allocation into simultaneously enrolling cohorts will alternate between cohorts.	Recommendation by SMC during Cohort #1 review. Allows potential to further explore safety, PK and PD activity; allocation specified to reduce bias
4.1.10, 4.1.11	Clarification	Clarified that venous or arterial blood may be used to monitor lactate and blood pH; abnormal venous blood pH results will require confirmation from arterial blood. Arterial blood lactate testing will also be used to confirm a potential DLT if an abnormal venous lactate level constitutes a DLT.	Recommendation by SMC during Cohort #1 review. Not previously specified. Clarification is to ensure accuracy of lactate and blood pH results while minimizing subject discomfort, as agreed with FDA
4.1.10, 4.1.11	Revised	Revised the requirements for monitoring subjects with elevated lactate and use in DLT definition of subjects with pH between 7.30 to 7.35 who remain asymptomatic	pH results in leukemia patients can be variable and are typically lower than normal subjects. Definition revised, using recommendations from SMC during Cohort #1 review and as modified based on FDA feedback.
4.1.10	Revised	Revised the lactic acid DLT definition to include presence of clinical symptoms and specify time frame (>24 hours) to determine second episode of elevated blood lactic acid	Recommendation by SMC during Cohort #1 review. Minimum time frame added to define 2 separate episodes of elevated lactate; clinical symptoms added to reduce potential to define

Section	Text	Amendments	Rationale for Change
			a DLT based on asymptomatic subjects with laboratory results that may be indicative of disease status only, as agreed with FDA
4.1.15, 4.2	Added	Additional PK and/or PD blood draws may be obtained ~every 4 days, when possible, for up to 4 weeks after last study drug administration in subjects who discontinue the study	Recommendation by SMC during Cohort #1 review. Allows potential to further explore PK and PD activity of IACS-010759 following discontinuation of study drug
4.2	Added	Additional PK blood draws on Days 8 and 14 of Cycle 2	Allows more frequent PK monitoring beyond Day 28, based on review of available cohort 1 PK data
4.2	Added	Further additional PK blood draws during Cycle 2 at the discretion of the Principal Investigators	Allows for additional PK monitoring during Cycle 2 if needed
4.2	Added	Additional PK blood draws, weekly for the first cycle after dose-escalation	Allows monitoring of PK levels after intra-subject dose escalation
4.2	Deleted/ Revised	Removed Cycle 1/Day 2, Day 4, Day 9, Day 17 PD assessments and changed Cycle 1/Day 10 to also collect PD 6 hours following dosing	Revised based on review of available cohort 1 PD data
5, 5.1.2, 5.2.1	Added, Clarification	Added SAS version to be used for statistical analysis; confirmed that a Statistical Analysis Plan will be prepared and finalized prior to data base lock. Clarified statistical analysis plans, including moving descriptions to different section of protocol.	Provides further information regarding planned statistical analysis; consistency and readability of protocol
1, 4.1.9.2, 4.1.11	Clarification	Corrected typographical errors	Consistency and readability of protocol
Amendment #3 (dated 14 December 2016)			
4.1.9, 4.2	Added	Added additional PK, lactate and blood pH testing following a dose reduction or interruption	Additional safety monitoring
4.2	Added	Added PD prior to dosing and 6 hours following dosing and PK, lactate and blood pH testing 6 hours following dosing on Cycle 1, Day 17 and Cycle 1, Day 22	Additional safety monitoring
4.1.10, 4.1.11, 4.2	Clarification	Clarified total CO_2 results will be used where bicarbonate testing is indicated	Consistency with site practice

Section	Text	Amendments	Rationale for Change
4.1.11	Revised	Updated anion gap reference range based on using total CO_2 results (where bicarbonate testing is indicated)	Use of total CO_2 results
4.2	Revised	ECOG testing to be performed only at Screening, Day 1 of each cycle, and End of Study visits	Consistency with site practice
4.2	Clarification	Clarified coagulation testing to include INR	Inadvertently omitted in previous version
4.2	Clarification	Clarified that blood hematology results below the level of quantitation will be recorded as 0	Informational
4.2	Clarification	Overall Response Rate assessment (as described in Section 5.2) included in study flowchart	Reminder to study personnel
4.2	Revised	Bone marrow assessments during additional cycles (beyond cycle 3) will be collected one day prior to D21 assessments	Allows bone marrow results to be available for review when performing D21 assessments
4.2	Revised	Corrected footnote 5 from 96 hours to 72 hours	Typographical error
Amendment #2 (dated 28 October 2016)			
4.2, 9.1.2, 9.1.6, 9.1.7	Clarification	All AEs including SAEs, should be collected, beginning from the time of the first protocol-specific intervention (study drug administration). New information regarding signs and symptoms that occurred prior to the first study medication dose on Day 1 should be recorded under the subject's Medical History.	Clarification of Adverse Event Reporting
Amendment #1 (dated 29 August 2016)			
Synopsis, 4.1.6, 4.1.7, 7.1	Clarification	Clarified cycle 1 length is 28 days (dosing occurs on Day 1 followed by continuous dosing starting on day 8)	FDA request
4.2	Added	Added CPK to chemistry testing	FDA request
4.2	Clarification	Clarified coagulation testing to include PT, PTT, fibrinogen	FDA request
4.2	Added	Added weekly laboratory testing during second cycle	FDA request
4.1.9.2, 4.2	Added	Added weekly laboratory monitoring during 1st cycle of increased dose for intra-subject dose escalation	FDA request
4.1.3, 6.1	Added	Added "no available treatment options with known benefit" to subjects to be enrolled in the expansion phase	FDA request
4.1.3, 6.1	Clarification	Clarified definition of relapsed or refractory for eligibility	FDA request
6.3	Revised	Revised lactate exclusion criterion	FDA request
7.2	Added	Added description for each capsule strength	FDA request
4.1.10	Revised	Revised DLT definition	FDA request

Section	Text	Amendments	Rationale for Change
4.1.11	Revised	Revised requirements for management of elevated lactate levels, including definition of lactic acidosis symptoms	FDA request
4.1.14, 4.1.7	Clarification	Clarified PK will be evaluated in each cohort prior to dose escalation	FDA request
4.1.7	Added	Added PK levels which will pause or stop dose escalation	FDA request
4.1.9	Revised	Revised dose modification criteria to permanently discontinue study drug in any subject that develops DLT related to lactic acid	FDA request
4.1.9.3	Revised	Revised intra-subject dose escalation criteria	FDA request
4.1.8	Revised	Revised stopping rule probability statement for expansion phase	FDA request
4.1.2, 4.1.7	Added	Added safety stopping criteria to encompass toxicities beyond cycle 1	FDA request
4.1.8	Revised	Revised the stopping boundaries for DLT monitoring to correct discrepancy	FDA request
7.1	Revised	Revised the food effect dose description to indicate the dose may be lower than R2PD	FDA request
4.2	Added	Added ECG monitoring at pre-dose and around the anticipated maximal plasma concentrations on Day 1, Day 14 and Day 28 of Cycle 1	FDA request
4.2	Revised	Research bone marrow sample will be collected at Screening rather than Cycle 1, Day 1	Reduce frequency of bone marrow sampling
6.1	Clarification	Revised inclusion criterion #9 to clarify the interval from prior treatment to time of initiation of study drug will be at least 2 weeks for biological/immune-based therapies	Clarification of wash-out period for prior treatment
8.1	Added	Added strong cytochrome P450 (CYP450) inhibitors or inducers as non-permitted concomitant medications	FDA request
2.1	Amended	Amended AML response rate reference	To ensure consistency with IND
Synopsis, 4.1.6	Clarification	Clarified that cycles occur on a continual basis	Readability of protocol
4.1.4	Clarification	Specified number of sites	Number of sites not previously provided
4.1.14	Revised	Revised Safety Monitoring Committee representatives description to specify study-specific Medical Monitor	Responsibility transferred to CRO
4.2	Clarification	Clarified in study flow chart which study days subjects are inpatient; timing of study drug administration; cycle days	Readability of protocol
4.2, 5.2	Clarification	Clarified bone marrow aspirate/biopsy will be performed clinically as indicated, at least once per 3 cycles	To ensure consistency of testing across study subjects
4.2, 10.2	Clarification	Clarified the QTc correction formula	Informational

Section	Text	Amendments	Rationale for Change
5.1.2	Added	Added name of clinical data base to be used for study data collection	New study information
7.2	Clarification	Clarified the planned starting dose capsule strength	Informational
9.1.2	Revised	Revised clinical data base and safety data base to be used for data collection	Responsibility transferred to CRO
9.1.3	Added	Added reference to recommended AE recording guidelines	Readability of protocol
9.1.7, 9.1.8	Revised	Revised safety reporting procedures and contact information	Responsibility transferred to CRO
Synopsis, 4.1.7, 5.2.2, 6.1, 10.2	Clarification	Corrected typographical errors	Consistency and readability of protocol
Original Protocol (dated 12 April 2016)			

2 Background Information

2.1 AML

Acute myeloid leukemia (AML) is a malignancy of immature granulocytes or monocytes. The malignancy is characterized by accumulation of leukemic blasts and blockade of normal bone marrow production resulting in thrombocytopenia, anemia, and neutropenia. There are approximately 13,000 new cases of AML per year in the United States, with an estimated 10,000 deaths occurring in the same time period[1]. Almost all newly diagnosed cases, as well as deaths, will be in adults[2]. Standard treatment for AML includes systemic combination chemotherapy to control bone marrow and systemic disease. Treatment is generally divided into an induction phase, to attain remission, and a consolidation/maintenance phase[2].

Traditional induction chemotherapy can produce complete remissions in most (50% to 75%) subjects with AML[3, 4]. Unfortunately, between 60% and 80% of subjects with AML (especially those with adverse cytogenetic features, adverse molecular mutations or antecedent hematological disorder) will be refractory or relapse after initial response to induction therapy relapse so only 20% to 30% will achieve long-term disease-free survival. For subjects with AML refractory to initial therapy or who relapse after a brief remission (< 12 months), outcomes are more dismal. We have previously reported a median OS of 3.8 months for subjects with AML who are refractory to induction therapy [5]. Similarly subjects with relapsed AML have a poor outcome with response rates ranging from 10% to 30% and overall survival <6 months with salvage therapy[6, 7].

These results emphasize the need to explore alternate salvage regimens for subjects with relapsed/refractory AML. The development of novel and effective anti-AML agents and/or combinations is crucial to improving the outcome of AML.

Tumors frequently rewire their metabolism to ensure a steady supply of metabolites for generation of ATP and for a biosynthesis of cell constituents. While aerobic glycolysis, also known as the Warburg effect, is a common metabolic alteration in cancer, recent studies indicate that some tumors are highly dependent on oxidative phosphorylation (OXPHOS) for survival [8-13]. Several recent reports demonstrate that oxidative metabolism generates intracellular energy and metabolic intermediates necessary to promote the growth of tumor cells [14-18]. It has previously been reported that leukemia cells have increased rates of fatty acid oxidation[16] and that inhibition of fatty acid oxidation rapidly inhibits oxygen consumption and sensitizes leukemia cells to induction of apoptosis, substantiating the idea that mitochondrial oxidative metabolism supports leukemia cell survival. Another ground-breaking study has demonstrated that leukemic stem cells (LSC) are unable to utilize glycolysis when mitochondrial respiration is inhibited, indicating that the maintenance of mitochondrial function is essential for LSC survival [15]. In contrast, normal murine [19] and human hematopoietic stem cells (HSC)[15] predominantly utilize glycolysis for energy homeostasis. Therefore, inhibiting oxidative phosphorylation in the context of AML could have therapeutic potential.

2.2 IACS-010579

2.2.1 IACS-010759 Preclinical Biology

IACS-010759 inhibits complex I of mitochondria oxidative phosphorylation (OXPHOS). IACS-010759 is a potent inhibitor of the proliferation of human cancer cells, including AML cell lines, human primary AML cells, and glycolysis-deficient NB-1 neuroblastoma cells. Both primary AML

cells and established cell lines demonstrated dose-dependent growth inhibition and reduction of cell viability in response to IACS-010759, with IC_{50} values ranging from 1-10 nM. Ectopic expression of the yeast complex I protein NDI-1 partially restored AML cell viability, indicating that the effects of IACS-010759 were mechanism-based *via* OXPHOS inhibition. In contrast to the potent effect of IACS-010759 on the viability of tumor cells, the compound had minimal effects on the viability of bone marrow cells obtained from healthy subjects, suggesting that the compound has a therapeutic window for tumor cells *vs.* normal leukocytes.

The sensitivity of NB-1 cells, which lack the gene that encodes the essential glycolytic pathway enzyme phosphogluconate dehydrogenase (PGD), to IACS-010759 was reduced upon ectopic expression of PGD. This suggests that the sensitivity of NB-1 cells to IACS-010759 is due to their inability to upregulate glycolysis in response to energy stress conferred by IACS-010759 treatment. This is consistent with the OXPHOS inhibitory mechanism of IACS-010759 and with the observed increase in potency of IACS-010759 to kill AML cells compared to normal bone marrow cells.

IACS-010759 inhibits tumor growth and extends survival in AML xenograft models. IACS-010759 caused dose-dependent tumor regression or substantial tumor growth inhibition (TGI) in both orthotopic and subcutaneous xenograft models with human AML and NB-1 neuroblastoma cells, while overall survival was increased in both primary AML and OCI-AML3 cell line orthotopic xenograft models.

In these *in vivo* efficacy experiments, increases in dose or shortening of the dosing interval corresponded to increases in efficacy, measured as TGI or regressions. Notably, in all studies, decreases in dosing frequency at a given dose correspond to decreases in efficacy, with QD dosing being more effective than intermittent dosing of the same dose of IACS-010759.

Trough plasma levels at steady state of 10-20 nM (5.6-11.3 ng/mL) were associated with efficacy in these xenograft studies, regardless of the dosing regimen. This concentration correlates well with the IACS-010759 concentrations of 1-10 nM that are required to inhibit cancer cell proliferation and to inhibit the OXPHOS pathway in cell based assays *in vitro*. Based on these preclinical efficacy studies, it seems reasonable to target sustained trough steady state plasma levels of 10-20 nM (5.6-11.3 ng/mL) IACS-010759 for efficacy in human clinical trials.

2.2.2 IACS-010759 Nonclinical Experience

The pharmacological, pharmacokinetic, and toxicological properties of IACS-010759 were characterized in a series of completed and ongoing nonclinical studies. These studies demonstrate that:

- IACS-010759 inhibits proliferation and reduces the viability of primary human AML samples treated *ex vivo* and in AML cell lines with IC_{50} values ranging from 1-10 nM, and has minimal effects on the viability of bone marrow cells obtained from healthy subjects. These studies suggest that IACS-010759 has a therapeutic window for tumor cells vs. normal leukocytes.
- IACS-010759 caused dose-dependent tumor regression or substantial tumor growth inhibition (TGI) in both orthotopic and subcutaneous xenograft models with human AML and NB-1 neuroblastoma cells. In addition, survival was increased in both primary AML and OCI-AML3 cell line orthotopic xenograft models. Several oral dosing regimens were explored in these studies, and efficacy was consistently observed with steady state trough plasma levels of 10-20 nM (5.6-11.3 ng/mL) IACS-010759.

- IACS-010759 had negligible inhibitory activity (estimated IC_{50} > 30 μM) at hERG K^+ channels and did not prolong the QTc interval in monkeys at doses up to 1.5 mg/kg/day for up to 28 days.
- IACS-010759 did not elicit central nervous system effects in rats treated with oral doses up to 2 mg/kg based on neurobehavioral parameters (functional observation battery).
- IACS-010759 exhibited low plasma clearance, a high volume of distribution, and a long half-life (42 to 57 hours) in mice, rats, dogs, and monkeys. Upon oral dosing, the compound was absorbed relatively slowly, with Tmax values in the range of 3 to 8 hours and bioavailability of ~100% in mouse and rat and ~36% in monkey.
- IACS-010759 exhibited low/moderate metabolic turnover following incubation with liver microsomes and hepatocyte preparations from mouse, rat, dog, monkey and human. No metabolites unique to human were identified. IACS-010759 was found to be a moderate competitive inhibitor of CYP 2C19 (IC_{50} = 4 uM), but did not inhibit any other CYP isoforms tested. No time dependent inhibition of CYPs 1A2 or 3A4 was observed.
- The potential for CYP enzyme induction by IACS-010759 could not be assessed in standard hepatocyte enzyme induction assays, likely because of the mechanism-based effects of IACS-010759 on oxidative phosphorylation. Therefore, the potential of IACS-010759 to reduce the levels of drugs metabolized by CYP450 enzymatic pathways is unknown.
- In transporter studies, IACS-010759 had no effect on BSEP-, MDR1-, OAT1-, OAT3-, OATP1B1-, OATP1B3- and OTC1-mediated probe substrate transport. IACS-010759 moderately inhibited the BCRP- and OCT-2 mediated probe transport by 27% and 36%, respectively, at 1 μM. IACS-010759 is likely a substrate of the BCRP and MDR1 transporters.
- A drug-drug interaction (DDI) study was conducted with IACS-010759 and pentagastrin or the histamine H2 blocker famotidine in dogs. Neither pentagastrin nor famotidine affected the plasma levels of IACS-010759 after oral administration, indicating low potential for DDI with drugs that affect stomach pH.
- IACS-010759 was nongenotoxic in a bacterial reverse mutation assay without or with metabolic activation, and in a bone marrow micronucleus test conducted after 28-days of oral administration in rats at doses up to 2 mg/kg/day, the highest dose tested.
- Single-dose IV administration of IACS-010759 to monkeys showed that sporadic emesis observed following oral and IV administration was a systemic rather than a local GI effect. Plasma levels of IACS-010759 associated with acute emesis were higher than those not associated with emesis.
- IACS-010759 was well tolerated in GLP-compliant 28-day oral toxicity studies in rats and monkeys at doses up to 1 mg/kg/day and 1.5 mg/kg/day, respectively. Higher doses in the 28-day studies and/or 14-day dose range-finding studies resulted in adverse effects in both species, including moribundity requiring euthanasia and/or mortality in rats at ≥2 mg/kg/day and in monkeys at ≥3 mg/kg/day. There were no treatment-related histopathological findings in tissue sections from the 28-day studies.
- C_{max} on Day 28 from pivotal toxicity studies was 61.3 ng/mL in rats and 99.3 ng/mL in monkeys at doses of 1 mg/kg/day and 1.5 mg/kg/day, respectively. These C_{max} values, which were observed at doses that were well tolerated for 28 days in each species, were notably higher than steady state trough plasma levels of 5.6 – 11.3 ng/mL at which efficacy was consistently observed in nonclinical xenograft models of human tumor cells. Because the human peak:trough plasma levels with daily oral dosing are projected to be <2-fold based on projected human clearance and on the preliminary data from cohorts 1 and 2 of the

present study, this represents a significant exposure multiple above the projected human exposure required for efficacy.

2.2.3 IACS-010759 Chemical Properties

IACS-010759 is available as a crystalline hydrochloride salt, with the chemical name 5-(5-methyl-1-(3-(4-(methylsulfonyl)piperidin-1-yl)benzyl)-1H-1,2,4-triazol-3-yl)-3-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazole hydrochloride salt.

The molecular formula of IACS-010759 hydrochloride salt is $C_{25}H_{25}F_3N_6O_4S.HCl$ and the molecular weight is 599.024 g/mole (562.564 g/mole as the free base). This compound has not yet been assigned a generic name.

3 Study Rationale

3.1 Rationale for IACS-010759 Dose Selection

The starting dose of IACS-010759 has been selected as the human equivalent dose corresponding to no more than 1/10 the no observed adverse effect level (NOAEL) in nonclinical toxicology studies. Additional considerations for dose selection include avoiding C_{max}-associated emesis and anticipation of achieving plasma levels associated with preclinical efficacy within a reasonable number of escalation steps. IACS-010759 was well tolerated in 28-day oral toxicology studies in the monkey and rat and the NOAEL in those studies were 1.5 mg/kg/day and 1 mg/kg/day, respectively. Based on these considerations, our projection is that a human starting dose of 0.5 mg will allow a thorough exploration of safety and tolerability in humans while minimizing the exposure of subjects to doses not anticipated to be effective. Using a model based on allometric scaling, a human dose of 0.5 mg, given once daily, would be anticipated to produce a C_{max} of ~2.3 ng/mL and to give a projected steady state exposure ratio, animal-to-human, of approximately 27-fold based on the 1 mg/kg/day dose in the rat and 43-fold based on the 1.5 mg/kg/day dose in the monkey for C_{max} and approximately 7-fold based on the rat and 11-fold based on the monkey for AUC. Therefore, the human starting dose of 0.5 mg of IACS-010759, administered orally once daily, would be anticipated to be safe and well tolerated, while allowing attainment early in the dose-escalation studies of doses that may be projected to show benefit in patients.

Limited PK data from subjects in cohorts 1 and 2 showed unexpected levels of accumulation of IACS-010759 throughout the dosing period, consistent with a model in which the clearance of IACS-010759 decreases exponentially with time, leading to an increasingly long terminal $T_{1/2}$ and accumulation upon multiple dosing. A mathematical model and simulation has been developed based on data from the subjects treated with IACS-010759 to date that predicts the observed human PK. Based on this model, a modified dosing regimen is being implemented for the dose escalation phase with cohorts 3-6 and for the dose expansion phase with cohort 7, consisting of an induction phase in which IACS-010759 is administered daily for up to 7 days, followed by a maintenance phase in which a lower dose is administered weekly to maintain steady state plasma levels (or as otherwise specified by the SMC based on safety, PK and PD data observed).

3.2 Rationale for Study Design

Current treatment options for relapsed or refractory AML reflect an unmet medical need and additional options for treatment are needed.

Preclinical data reviewed above strongly suggest a robust antitumor activity with IACS-010759 in AML. The current study focuses on evaluating the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D) and safety profile of IACS-010759 and preliminary clinical efficacy in subjects with confirmed relapsed or refractory AML and no available treatment options with known benefit.

The results from this study will form the basis for decisions for future studies.

4 Experimental Plan

4.1 Study Design

4.1.1 Study Phase

Phase 1 study with a dose-escalation phase followed by an expansion phase.

4.1.2 Enrollment/Randomization

This open label study will employ a sequential-cohort, non-randomized, single site enrollment. The study will be under ongoing review by a Safety Monitoring Committee (see section 4.1.14).

In the dose-escalation phase, all subjects in a cohort will be monitored for DLT for the first cycle before proceeding with subsequent cohorts. To assess toxicities that may occur beyond cycle 1, cohorts of up to 6 subjects will be assessed following completion of 4 cycles of study drug. If two or more subjects in the cohort did not receive at least 80% of the planned dose due to adverse events, dose escalation will be paused and an evaluation will be performed.

4.1.3 Subject Population

For complete subject eligibility please see section 5.

Dose-escalation phase: Subjects with confirmed relapsed or refractory AML and no available treatment options with known benefit.

Expansion phase: Subjects with relapsed or refractory AML who have failed therapy with up to one prior salvage regimen and no available treatment options with known benefit.

Exception: stem cell transplant [SCT] or stem cell therapy for subjects who previously underwent SCT/stem cell therapy, and are currently in remission will not be considered a salvage regimen.

Relapsed or refractory status is defined by the failure of at least one prior cycle of chemotherapy (including but not limited to cytotoxic chemotherapy, hypomethylator therapy, immune-based therapy, stem cell transplant or stem cell therapy, FLT3-inhibitor therapy, investigational therapy, and others). Patients in first relapse and less than 12 months from diagnosis [short first remission] or in second or later relapse are eligible.

4.1.4 Number of Sites and Subjects

2 to up to 48 subjects will be enrolled at one site.

4.1.5 Sample Size Considerations

The dose-escalation phase of the study will enroll 3-6 subjects in each cohort, based on a 3+3 dose-escalation design to assess the MTD level. A maximum of 36 subjects will enroll in the dose-escalation phase.

A maximum of 18 subjects will enroll in the expansion phase (12 additional subjects and the 6 subjects from the dose-escalation phase at the cohort of the highest dose level shown to be well tolerated or the RP2D). The expansion phase sample size of 18 subjects is not based on a formal sample size calculation. Rather, 18 subjects are deemed to be sufficient for the assessment of safety and tolerability as the primary objective and the exploration of clinical anti-tumor activity and other secondary and exploratory endpoints.

4.1.6 Treatment Cohorts and Treatment Schema

In cohorts 1 and 2, IACS-010759 was administered orally daily on a continual 21-day schedule (1 cycle = 21 days of daily dosing), with the exception that the first cycle for each subject contains a 7-day single dose lead-in (first cycle = 28 days). Starting on day 8 of cycle 1 for subjects enrolled in cohorts 1 and 2, dosing is on a 21 day schedule until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment prematurely occur as defined in Section 4.1.9.

Based on PK modeling of data from cohorts 1 and 2, the dose regimen for cohort 3 and subsequent cohorts will change to include an induction phase with daily dosing, followed by a maintenance phase at a dose sufficient to maintain the steady state levels achieved during the induction phase. In these cohorts, IACS-010759 will be administered orally daily (up to 7 days) during the induction phase(Cycle 1, Days 1-7). Starting on day 8 of cycle 1 for all cohorts, maintenance dosing will be administered on a 21-day schedule until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment prematurely occur as defined in Section 4.1.9.
The planned dose levels are given in Table 1 and 2, below:

Table 1: Dosing schema for Cohorts 1 and 2

PHASE	COHORT	NO OF SUBJECTS	IACS-010759 DOSE LEVEL *
Dose-escalation	Cohort 1	3-6	0.5 mg
	Cohort 2	3-6	1 mg

*Intermediate doses of IACS-010759, not to exceed 8 mg, not listed above may also be pursued with SMC approval, depending on the safety, PK and PD data observed.

Table 2: Revised dosing schema for Cohorts 3-6 (Dose-Escalation) and Cohort 7 (Dose Expansion)

PHASE	COHORT	NO OF SUBJECTS	INDUCTION DOSE* (FREQUENCY#)	MAINTENANCE DOSE* (FREQUENCY#)
Dose-escalation	Cohort 3	3-6	2 mg (daily, Cycle 1 Day 1-7)	0.5 mg (once per week)
	Cohort 4**	3-6	2.5 mg (daily, Cycle 1 Day 1-7)	1.0 mg (three times per week)
	Cohort 5	3-6	2.5 mg (daily, Cycle 1 Day 1-5)	1.5 mg (three times per week)
	Cohort 6	3-6	3 mg (daily, Cycle 1 Day 1-5)	2 mg (three times per week)
Expansion	Cohort 7	12	RP2D	RP2D

*Intermediate induction or maintenance doses of IACS-010759 may be pursued with SMC approval, not to exceed 6 mg, and
alternative duration of induction doses or other maintenance schedules not listed above may also be pursued with SMC approval depending on the safety, PK and PD data observed.
**Following their review of Cohort 3, the SMC recommended implementation of the following dose schedule for

subjects who enroll in Cohort 4 of the study:

Induction dose: 2.5 mg, administered daily, Cycle 1 Day 1 through Day 7

Maintenance dose: 1 mg, administered 3x/week (for a total weekly dose of 3 mg) with the first maintenance dose starting on Cycle 1 Day 8

4.1.7 Dose-escalation

A standard 3+3 dose-escalation design will be used to determine MTD. The potential dose schedule is shown in section 4.1.6. In the first cohort, as a safety precaution, each new subject began treatment only after the safety analysis for DLTs and evaluation of PK data during the first cycle (28 days) was completed for the previous subject. In subsequent cohorts of the dose-escalation phase, new subjects will be entered and treated only after the previous subject has been treated with IACS-010759 for up to 7 days (e.g., has completed the induction phase) and DLT safety analysis for each subject will be performed after completion of cycle 1. PK data will be monitored for each subject and evaluated for each cohort during the study and plasma levels will be considered when making dose escalation decisions.

The following dose-escalation rules will be applied:

- If 0 out of the 3 subjects have a DLT, the next cohort may be started.
- If 1 out of the 3 subjects has a DLT, an additional 3 subjects will be enrolled in the same cohort. If none of these 3 additional subjects have a DLT after being observed for 28 days (i.e., cycle 1), the next dose escalation cohort may be started.
- If 2 or more out of 6 subjects in Cohort 1 develop a DLT, enrollment will cease immediately and the study will be halted. No MTD can be determined.
- If 2 or more out of 6 subjects in the following Cohorts (2-6) develop a DLT, enrollment into the cohort will cease, and the prior cohort's dose level will be deemed as MTD level. All subjects from the non-tolerated cohort will be de-escalated to the prior cohort's dose level.
  If at least 2 of 3 or 2 of up to 6 patients experience a DLT at a given dose, then the MTD has been exceeded (stopping dose). Once the MTD has been exceeded, treat another 3 patients at the previous dose if there were only 3 patients treated at that dose.

During dose escalation, if necessary, cohorts may be expanded in the absence of a DLT, to a total of up to 6 subjects to further explore safety, PK and PD activity of IACS-010759 at each dose level with the approval of the SMC. Such an expansion may occur concurrently with dose escalation to the next dose level. A predetermined allocation to cohorts that minimizes selection bias will be used when enrolling into two open cohorts simultaneously. Allocation to simultaneously open cohorts will be performed in an alternating random manner, based on entry into the study. During dose escalation, intermediate (including induction or maintenance) doses and alternative duration of induction doses or other maintenance schedules of IACS-010759, not to exceed 6 mg, may also be pursued with SMC approval, depending on the safety, PK and PD data observed.

The dose escalation phase of the study will be paused after the dose at which the mean steady state plasma levels, measured as pre-dose concentrations on Day 28 for cohorts 1 and 2 and as pre-dose concentrations on Day 8 (e.g. the end of the induction phase) for cohorts 3 onwards, reach levels of ≥20 nM (11 ng/mL). A full review of the safety, PK and efficacy data from that

cohort will be performed and escalation may be continued if the MTD has not been reached, and the Sponsor obtains agreement with FDA to continue dose escalation.

The dose escalation phase of the study will stop after the dose for which the mean Cmax on Day 28 for cohorts 1-2 or Day 7 for cohorts 3 and onwards is ≥100 nM, or after the dose for which the mean steady state concentration for the cohort, as measured on the last day of any 21 day Cycle, is ≥100 nM, whichever dose is lower.

To assess toxicities that may occur beyond cycle 1, cohorts of up to 6 subjects will be assessed following completion of 4 cycles of study drug. If two or more subjects in the cohort did not receive at least 80% of the planned dose due to adverse events, dose escalation will be paused and an evaluation will be performed.

Once the MTD has been established or the dose-escalation completed without identifying a MTD, the RP2D will be defined based on an assessment the safety, pharmacokinetic (PK), pharmacodynamic (PD), biomarker, and response data.

At the discretion of the sponsor, dose-escalation may be stopped before an MTD is reached. In this case, the RP2D may be chosen based on an assessment of the safety, PK, PD, biomarker, and response data evaluable up to that time. An MTD does not have to be reached to expand a dose cohort if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk. Upon completion of the dose-escalation, the cohort with either the highest dose level shown to be well tolerated or the RP2D will be expanded to a total of 6 subjects (if not already expanded to 6 subjects due to either observation of a DLT or to further explore safety, PK and PD activity of IACS-010759 at that dose level).

Late onset DLTs that could not be taken into consideration prior to scheduled dose escalations will be ad-hoc evaluated on a case-by-case basis, and may lead to enrollment of additional subjects in specific cohorts or to revision of the previously determined MTD.

4.1.8 Expansion Phase

Subjects in the expansion phase will be treated at the RP2D level determined in the dose-escalation phase.

The primary objective of the expansion phase is to determine safety of IACS-010759.

Additionally, as part of the expansion phase, the effect of a high fat meal on the PK of IACS-010759 (Food Effect) will be evaluated in a total of 6 subjects (Food Effect cohort), as described in Section 7.1. After the first 6 subjects have been enrolled in the expansion cohort, the next 6 subjects will be enrolled in the Food Effect cohort.

To evaluate safety, the method of Thall, Simon and Estey [20] will be used for monitoring DLTs occurring in the first cycle. The probability of DLT is denoted by P_T. We assume P_T ~ beta (0.4, 1.6). Our stopping rule is given by the following probability statement: $Pr(P_T > 0.20 \mid data)>0.80$.

That is, if at any time during the study we determine that there is more than 80% chance that the unacceptable toxicity rate is more than 20% during the expansion phase, then the enrollment will be stopped. Subjects will be monitored by a cohort size of 6 during the expansion phase according to the following stopping boundaries for DLTs, starting from the 12th

subject. The monitoring rule for DLTs, based on these assumptions and monitoring conditions is found in Table 3. For example, accrual in the expansion phase will cease if 4 or more subjects experience DLTs among the first 12 subjects. The operating characteristics are summarized in Table 4. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center was used to generate the toxicity stopping boundaries and the operating characteristics tables.

Table 3 Stopping boundaries for DLT monitoring

# Subjects evaluated	12	18
# Subjects with DLTs	4-12	6-18

Table 4 Operating characteristics of toxicity monitoring

True DLT Rate	Early Stopping Probability	Average Sample Size
0.10	0.0256	17.8
0.15	0.0922	17.4
0.20	0.2054	16.8
0.25	0.3512	15.9
0.30	0.5075	15.0

4.1.9 Dosing Adjustments, Delays and Discontinuations

IACS-010759 dose reduction/interruption/discontinuation decisions should be based on the CTCAE version 4.03 of the toxicity and according to the guidelines shown below. If toxicity is not covered in the table, doses may be reduced or held at the discretion of the investigator for the subject's safety. Additional PK, blood pH and lactate testing will be performed following a dose reduction or resumption of dosing following a dose interruption, as described in Section 4.2. IACS-010759 should be permanently discontinued in any subject that develops DLT due to lactic acid.

If a dose interruption occurs at the end of a cycle, the next cycle will be delayed and start on the first day of dosing of the next cycle. Dose interruptions which occur during a cycle will not change the study days during the cycle.

4.1.9.1 *IACS-010759 Dose Adjustments for Drug-Related Hematological AEs*

- Subjects with acute leukemias usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemias. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 cycles and/or in the presence of residual leukemia. After that, treatment interruptions and dose adjustments may be considered according to the following guidelines only when there is no evidence of residual leukemia.

- Subjects with a response (e.g., no evidence of residual leukemia or cytopenias not considered to be related to leukemia) and pre-cycle counts of neutrophils >1.0 x 10^9/L and platelets >50 x 10^9/L who have sustained low counts of neutrophils <0.5 x 10^9/L or a platelet count <20 x 10^9/L for more than 2 consecutive weeks in the current cycle, may have the treatment with IACS-010759 interrupted at the discretion of the treating physician after discussing with the Principal Investigator (PI) until neutrophils recover to ≥0.5 x10^9/L and platelets to ≥30 x 10^9/L. If prolonged myelosuppression defined as ANC < 0.5 x 10^9/L and

platelets < 20 x10^9/L (more than 6 weeks) with evidence of a hypocellular marrow (marrow cellularity less than 5% without evidence of leukemia) is observed, IACS-010759 will be discontinued in these subjects. Delays in the start of subsequent cycles greater than 6 weeks will be acceptable only for subjects who are deriving clinical benefit and after discussion with the Principal Investigator (PI) of potential risk/benefit ratio and complete documentation of the degree of clinical benefit and reason for continuation on this regimen.

- If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts or evidence of leukemia, treatment may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions of IACS-010759 in these subjects should be considered on an individual case and discussed with the PI and the sponsor.

- Subjects with a response (no marrow evidence of leukemia) and pre-cycle counts of neutrophils <1x10^9/L and platelets <50 x10^9/L may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions in these subjects should be considered on an individual case and discussed with the PI and the sponsor.

4.1.9.2 *IACS-010759 Dose adjustments for Non-Hematologic Drug-Related AEs*

Dose adjustments for AEs will be performed using dose levels suggested in Table 1 and 2 in Section 4.1.6. Thus, if cohort 6 is established as the MTD, one and two dose level reductions of IACS-010759 will be the doses specified in cohort 5 and cohort 4, respectively. If the MTD is below cohort 3 further dose reduction levels of IACS-010759 will be defined before moving to the expansion phase of the study to allow for the below specified dose-reductions.

Table 5: Dose adjustments for non-hematologic drug-related AEs, clinically significant in the opinion of the investigator

Grade	Occurrence	Dose modification
1 or 2	Any time	No dose reduction.
3 (Persistent grade 2: Consider similar dose adjustments if persistent and not responding to optimal management in the opinion of PI and treating physician)	1st and 2nd time	Hold treatment with IACS-010759. Resume IACS-010759 at pre-interruption dose if recovery to ≤ Grade 1 or baseline occurs within 14 days. If toxicity persists for >14 days, hold therapy and resume at ONE dose level below current dose for IACS-010759 ONLY after recovery of toxicity to ≤ Grade 2. Dose re-escalation to prior dose of IACS-010759 is not permitted.
	3rd time	Stop treatment with IACS-010759 and discontinue subject. (For subjects with clinical benefit/response from IACS-010759 we will consider continuation if toxicities resolve to ≤ grade 1 and with proper dose adjustments after consultation with the PI and the sponsor)
4	Any time	Stop treatment with IACS-010759 and discontinue subject. (For subjects with clinical benefit/response from IACS-010759 we will consider continuation if toxicities resolve to ≤ grade 1 and with proper dose adjustments after consultation with the PI and the sponsor)

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor in specific cases.

4.1.9.3 *Intra-Subject Dose Escalation*

Intra-subject dose escalation of IACS-010759 (in accordance with the dosing schema in Table 1 and 2) will be permitted provided:

- Subject has completed ≥2 cycles at their current dose level and has not achieved a CR or Cri
- Subject has not experienced any grade 3 or higher non-hematologic drug-related toxicity, and

Subject has not experienced DLT,

- The dose may be escalated by one dose level no more frequently than every 2 cycles.
- The escalated dose level must have been fully evaluated and shown not to exceed the MTD (0 DLT of 3 or ≤1 DLT of 6)

If an intra-subject dose escalation occurs, laboratory monitoring will be increased to weekly during the first cycle of the increase dose.

4.1.9.4 *Other Allowable Modifications of Dose Schedules*

Other modifications of dose schedules than the above will be allowed within the following guidelines:

- Further dose reductions can be made to keep clinically significant toxicities grade < 2. Dose adjustments by more than 1 dose level at a time (e.g., from cohort 6 dose to cohort 4 dose) can be considered when judged in the best interest of the subject (e.g. severe myelosuppression, lactic acidosis) when the toxicity has resolved. The reason for this reduction will be discussed with the PI or Co-PI and documented in the medical record.
- Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI, sponsor and proper documentation of the rationale.

4.1.10 DLT, MTD and RP2D definitions

The MTD is defined as the highest dose studied for which the observed incidence of DLT is less than 33%. Frequencies of toxicities will be tabulated according to the NCI Common Toxicity Criteria version 4.03.

The RP2D will be determined based on the safety data and all available correlative data from the escalation phase by the Safety Monitoring Committee.

Dose-limiting toxicity (DLT) is defined as a clinically significant non-hematologic adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and is possibly, probably or definitely related to the study drug and occurring during the first cycle (21 days) on study that meets any of the following criteria:

- All Grade 4 non-hematologic toxicities of any duration
- All grade 3 non-hematologic toxicities. Exceptions are as follow:
    - Grade 3 nausea, vomiting and diarrhea that does not require hospitalization or TPN support and can be managed with supportive care to ≤ grade 2 within 48 hours.
    - Grade 3 electrolyte abnormalities that are corrected to ≤ grade 2 within 24 hours.
- Lactic Acid:
    - Blood lactic acid levels [>4.0 mmol/L]) and decreased blood pH (>7.2 to <7.30) and no clinical symptoms of metabolic acidosis [nausea, vomiting, generalized muscle weakness, tachycardia, hypotension and rapid breathing] and normal potassium maintained in two consecutive laboratory assessments separated by >12 hours despite management as described in Section 4.1.11. To qualify as a DLT, the blood lactic acid levels [>4.0 mmol/L]) and decreased blood pH (<7.30) should be confirmed on arterial blood draws. Patients who develop pH between 7.30 - 7.35 while on therapy who are asymptomatic, and have other etiologies for metabolic acidosis ruled out, may be permitted to continue on treatment. These patients will have an increased monitoring of pH and lactate levels minimally at approximately 6 hours, 12 hours and 24 hours, until normalization of pH is established, so as to rule out any worsening acidosis. Patients with a baseline normal pH (>7.35) and no clinical evidence of progressive leukemia (defined by >50% blasts in the bone marrow or peripheral blood, white count >20K, requiring hydroxyurea to control WBC counts, or new extramedullary leukemia) who develop acidosis that fulfills the criteria for a DLT during the DLT window, should be considered a DLT.
    - Blood lactic acid levels [>4.0 mmol/L]), decreased blood pH (<7.35 if the

baseline pre-therapy pH was >7.35 or blood pH <7.30 if the baseline pre-therapy pH was ≤7.35), with bicarbonate >LLN and anion gap elevated, abnormal potassium and/or, in the opinion of the investigator, the subject is symptomatic for lactic acidosis [nausea, vomiting, generalized muscle weakness, tachycardia, hypotension and rapid breathing (Section 4.1.11, point 3). To qualify as a DLT, the blood lactic acid levels [>4.0 mmol/L]) and decreased blood pH <7.35 if the baseline pre-therapy pH was >7.35 or blood pH <7.30 if the baseline pre-therapy pH was ≤7.35), should be confirmed on arterial blood draws.

- Second episode of blood lactic acid level > 4.0 mmol/L, confirmed as lactic acid level > 4.0 mmol/L on arterial blood, separated by >24 hours blood draw, in the presence of clinical symptoms attributable to lactic acidosis [nausea, vomiting, generalized muscle weakness, tachycardia, hypotension and rapid breathing]

Myelosuppression and associated complication are expected events during leukemia therapy. Only prolonged myelosuppression, as defined as ANC <500 through day 42 or later (6 weeks) from start of therapy without any evidence of leukemia, will be considered in defining the MTD and DLT.

4.1.11 Assessment of Elevated Lactic Acid Levels

Lactic acidosis is a potential mechanism-based side effect resulting from inhibition of mitochondrial oxidative phosphorylation by IACS-010759 and has been observed at high doses in preclinical studies. Peripheral venous or arterial lactate levels will be monitored during the trial as detailed in section 4.2 study flowchart. (Note: Venous or arterial blood may be used to monitor lactate and blood pH. Arterial blood lactate testing will also be used to confirm a potential DLT if an abnormal venous lactate level constitutes a DLT.)

A recent review by Kruse et al. [21] on the measurement of lactate concluded that peripheral venous lactate levels are highly correlated with arterial blood lactate levels. In the setting of elevated lactate, a complete physical exam and directed history will be performed to rule out other causes of elevated lactate levels (see appendix 9.1)

Subjects will have their lactic acid levels, blood pH as well as electrolytes including chloride and bicarbonate (reported as total CO_2) levels measured according to section 4.2. Subjects with lactate levels >4 mmol/L and pH <7.30 and symptoms attributable to lactic acidosis [nausea, vomiting, generalized muscle weakness, tachycardia, hypotension and rapid breathing] will be hospitalized for monitoring of lactate levels and pH, electrolytes and symptoms of lactic acidosis [nausea, vomiting, generalized muscle weakness, tachycardia, hypotension and rapid breathing] for a minimum of 24 hours. The lactic acid and blood pH levels will be assessed as follows:

1. If lactic acid is > ULN but below 4.0 mmol/L, pH >7.35 and subject is asymptomatic, treatment can be continued. Patients with pH between 7.30 - 7.35 who are asymptomatic, and have other etiologies for metabolic acidosis ruled out, may be permitted to continue on treatment. These patients will have an increased monitoring of pH and lactate levels minimally at 6 hours, 12 hours and 24 hours, until normalization of pH is established, so as to rule out any worsening acidosis. Patients with a baseline normal pH (>7.35) and no clinical evidence of progressive leukemia (defined by >50% blasts in the bone marrow or peripheral blood, white count >20K, requiring hydroxyurea to control WBC counts, or new extramedullary leukemia) who develop acidosis that fulfills the criteria for a DLT during the DLT window, should be considered a DLT.

2. If lactic acid >ULN but below 4.0 mmol/L, and subject is symptomatic (nausea, vomiting, generalized muscle weakness, tachycardia, hypotension and rapid breathing), treatment should be interrupted as indicated and lactic acidosis workup performed.
3. If lactic acid is above 4.0 mmol/L, blood pH ≥7.35 and bicarbonate (reported as total CO_2) is <LLN, potassium is normal and anion gap <14, and subject is asymptomatic, dosing should be interrupted. Lactic acid and blood pH and electrolytes should be reassessed within 12 hours on arterial and/or venous blood draw until the lactic acid level is <4.0 mmol/L. Once the lactic acid level is <4.0 mmol/L on arterial and/or venous draw, the subject can continue therapy at the discretion of the investigator.
4. If lactic acid is above 4.0 mmol/L, blood pH <7.35 if the baseline pre-therapy pH was >7.35 or blood pH <7.30 if the baseline pre-therapy pH was ≤7.35) and the bicarbonate (reported as total CO_2) is <LLN and anion gap is elevated, and/or the subject is symptomatic, this will be considered a DLT. Treatment should be interrupted and lactic acidosis workup performed (See Section 7.2.3).

Anion gap via venous blood collection can be calculated as follows: Anion Gap= [Na+] - [Cl-] - [total CO_2]; normal range 4-14 mmol/L.

Anion gap via arterial blood collection can be calculated as follows: Anion Gap= [Na+] - [Cl-] - [***HCO3-***]; normal range 8-16 mEq/L.

Symptoms of lactic acidosis include nausea, vomiting, generalized muscle weakness, tachycardia, hypotension and rapid breathing. Subjects with clinical symptoms concerning for lactic acidosis should have an arterial blood gas assessment. Lactic acidosis is characterized by an elevated blood lactate concentration [>4.0 mmol/L]), decreased blood pH (<7.35), and electrolyte disturbances with an increased anion gap.

4.1.12 Subject Withdrawal

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

1. Clinically significant progressive disease, or
2. Intercurrent illness that prevents further administration of treatment, or
3. Subject request, or
4. General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator, or
5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.

It is planned that up to a total of 12 cycles of therapy will be administered for subjects deriving benefit from this regimen. Continuation of therapy for subjects completing 12 cycles of therapy may be considered on a case-by-case basis after discussion with the Principal Investigator.

4.1.13 Subject Evaluability and Replacement

In the escalation phase, subjects who are not considered fully evaluable per protocol for the primary objective of safety and tolerability per Section 4.3 will be replaced. Subjects who have taken 75% or more of the planned IACS-010759 treatment in cycle 1 will be considered evaluable for MTD. Subjects who have taken less than 75% of planned medication in cycle 1, but who came off study due to a DLT will also be considered evaluable.

4.1.14 Safety Monitoring and Study Stopping Rules

Safety monitoring, including analysis of PK, will be performed by a Safety Monitoring Committee, consisting of the Principal Investigator (and co-investigators as needed) and sponsor representatives (e.g., a designee from the IND Office) and the study-specific Medical Monitor. Additional investigators and staff shall participate in reviews as indicated.

An Independent Data Monitoring Board will not be utilized for this open label study.

4.1.14.1 *Study Stopping Rules*

The Safety Monitoring Committee has the right to recommend to terminate or alter the study design of this clinical study at any time. The principal investigator will be involved in any decisions regarding terminating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment. MD Anderson/IND Office (as the sponsor) has the right to terminate the clinical study at any time.

Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to subjects
- Data recording is significantly inaccurate or incomplete
- Study site personnel are noncompliant with study procedures

4.1.14.2 *Protocol Violations and Deviations*

Protocol violations are defined as significant departures from protocol-required processes or procedures that affect subject safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following classes:

- Enrollment criteria
- Study activities (missed evaluations or visits) except for those allowed per protocol
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay; or discontinuation criteria
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the subject will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule, occasional missed required research samples such as correlative assays.

4.1.15 Follow-Up at Treatment Discontinuation or Early Withdrawal

Subjects who discontinue treatment for any reason should complete end-of-treatment procedures when possible. End of treatment procedures will include a physical examination, CBC with differential and platelets and chemistry. A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. Although treatment will be discontinued at that time, all subjects who do not die, withdraw consent for follow-up, or become lost to follow-up, will remain on study for

follow-up evaluations. Subject will be followed for possible delayed emergence of IACS-010759 related toxicity at least 30 days after the last protocol treatment. Subjects who discontinue the study will be requested to return for additional PK and/or PD blood daws, approximately every 4 days, when possible, for up to 4 weeks after the last study drug administration to further explore the PK and PD activity of IACS-010759 following discontinuation of study drug. The 30-day (+/-7 days) follow-up visit will be scheduled as a clinic visit for clinical evaluation and physical examinations. If the subject cannot make it to the site for this visit, the required follow up treatment procedures may be performed by a local physician and the records forwarded to the site. The research nurse will also contact the subject by telephone and obtain a verbal assessment of the subject's condition. The phone conversation will then be documented in the subject's charts.

4.1.16 Long-Term Follow-Up

Subjects who achieve any response will be followed for overall survival and response duration for up to 12 cycles. Patients who are responding well to therapy may continue therapy beyond 12 cycles after approval from the PI and sponsor.

If the disease appears to be responding to the study drug, a member of the study staff will call the subject once every 3-6 months for up to 5 years to assess the subject's health.

4.2 Study Flowcharts

Cohorts 1 and 2

	Screen	Cycle 1 (28 days)											Cycle 2 (21 days)				Cycle 3 (21 days)		Additional Cycles (21 days)		End of Study or Early Termination
Study Day	-7 to -1	1*+	2*	4	8*	9*	10*	12*	14*	17	22	28	29	36	42	49	50	70	Every 21 days		30 after last Dose
Name of Cycle Day		C1 D1	C1 D2	C1 D4	C1 D8	C1 D9	C1 D10	C1 D12	C1 D14	C1 D17	C1 D22	C1D 28	C2 D1	C2 D8	C2 D14	C2 D21	C3 D1	C3 D21	CX D20	CX D21	51
+/- days allowable										1	1	1	2	2	2	2	3	3	4	4	7
Study Drug§		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease Assessment																					
Bone marrow aspirate and/or biopsy¥	X											X						X	Every 2-3 cycle		X
Overall Response Rate‡												X						X		X ‡	X
Study Procedures & Examinations																					
Eligibility Assessment & Informed Consent	X																				
Demographics[A]	X																				
Medical history[B]	X																				
MUGA/ECHO	X																				
12-lead ECG (QTcF)	X	X[2]			X				X[2]		X	X[2]									
Phys. Exam (inc. weight)	X	X			X		X		X	X	X	X	X			X	X	X		X	X
ECOG	X	X											X				X			X	X
Vital Signs (Temp., HR, BP, RR)	X	X[2]	X[4]	X[5]	X[2]	X[1]	X[1]	X[1]	X[2]	X[3]	X[3]	X[2]	X[3]	X[6]	X[6]	X[3]	X[3]	X[3]		X	X
Concomitant Medication[C]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Adverse Events[D]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Labs																					
Pregnancy test	X																				
Blood Hematology[E, I, J]	X	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X	X			X	X	X		X	X
Chemistry[F, I]	X	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X	X	X[6]	X[6]	X	X	X		X	X
Coagulation, lipase, amylase & urinalysis[G, I]	X	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X	X	X[6]	X[6]	X				X	X
Lactate and blood pH [I, K]	X	X[1]	X[4]	X[5]	X[1]	X[3]	X[3]	X[1]	X[1]	X[1]	X[1]	X[1]	X[3]	X[6]	X[6]	X[3]	X[3]	X[3]		X	X
Research Labs																					
Blood collection- pharmacodynamics[H]	X	X[1]			X[1]		X[1]		X[1]		X[1]	X[1]									X[L]
Research Bone marrow aspirate/or biopsy	X											X									

Pharmacokinetics Blood samples [I,K,M]		X[2]	X[4]	X[5]	X[2]	X[1]	X[1]	X[1]	X[2]	X[1]	X[1]	X[2]	X[3]	X[6]	X[6]	X[3]	X[3]	X[3]			X[L]

Notes and abbreviations provided on following page.

[A] including Date of Birth; sex; height; race; ethnicity
[B] including oncology history, radiation history
[C] name, indication, dose, route, start and end dates
[D] starting or worsening after study drug administration (signs and symptoms occurring prior to the first dose of study medication on Day 1 should be recorded under the subject's Medical History).
[E] complete blood count, differential, platelets
[F] glucose, total protein, albumin, electrolytes [sodium, potassium, chloride, total CO_2], calcium, phosphorus, magnesium, uric acid, bilirubin (total, direct), SGPT (ALT) or SGOT (AST), alkaline phosphatase, creatinine, blood urea nitrogen, CPK
[G] PT, PTT, fibrinogen, INR
[H] Oxygen consumption, metabolites, protein, mRNA analysis
[I] To be performed weekly during the first cycle of the increased dose for any intra-subject dose escalation
[J] For purposes of data collection, test results below the limit of quantitation will be reported as "0"
[K] If the Investigator determines that the dose of study drug should be interrupted, additional PK, lactate and blood pH assessments will be collected pre-dose (within 2 hours of dosing) and 6 hours +/- 30 minutes post study drug administration upon resumption of dosing. If the dose of study drug is reduced, additional PK assessments will be collected pre-dose (within 2 hours of dosing) and 2, 4, 6, 8, 12 (+/- 15 mins) and 72 hours (+/- 4 hours) after starting the reduced study drug dose.
[L] Additional PK and/or PD draws from peripheral blood may be obtained ~every 4 days, when possible, for up to 4 weeks after last study drug administration in subjects who discontinue the study.
[M] In addition to the time points indicated in the Table, additional draws from peripheral blood for PK analysis may be obtained during Cycle 2 and beyond at the discretion of the Investigator.

[1] collected pre-dose (within 2 hours of dosing) and 6 hours +/- 30 minutes post study drug administration
[2] collected pre-dose (within 2 hours of dosing) and 2, 4, 6, 8 and 12 hours (+/- 15 mins) post study drug administration
[3] collected pre-dose (within 2 hours of dosing)
[4] collected 24 hours +/- 2 hours post study drug administration
[5] collected 72 hours +/- 4 hours post study drug administration
[6] collected pre-dose

* Treatment will be administered as an inpatient for 24 hours on Day 1 of Cycle 1 and then starting again on Day 8 for the next 7 days.
+ Subjects enrolled in the Food Effect group will consume a high fat meal within 30 minutes prior to study drug administration on Day 1 blood sample collection.
§ Study drug will be administered without food, at least 1 hour before and at least 2 hours after eating, with the exception of Day 1 of Cycle 1 for subjects enrolled in the Food Effect group.
¥ Bone marrow aspirate/biopsy will be performed as clinically indicated, at least once every 3 cycles.
‡ Overall Response Rate (ORR) assessment will be performed on the same schedule as bone marrow aspirate/biopsy (every 2-3 cycles during additional cycles). ORR definitions are provided in Section 5.2.2.

Cohorts 3-4 Dose-Escalation

	Screen	Cycle 1 (21 days)									Cycle 2 (21 days)					Cycle 3 (21 days)		Additional Cycles (21 days)		End of Study or Early Termination
Study Day	-7 to -1	1+	2	4	7*	8	12	15	17	21	22	29	36	37	42	43	63	Every 21 days		30 after last Dose
Name of Cycle Day		C1 D1	C1 D2	C1 D4	C1 D7	C1 D8	C1 D12	C1 D15	C1 D17	C1 D21	C2 D1	C2 D8	C2 D15	C2 D16	C2 D21	C3 D1	C3 D21	CX D20	CX D21	51
+/- days allowable				1	1	1	1	1	2	+2	1	1	1	2	1	3	3	4	4	7
Study Drug§		INDUCTION				MAINTENANCE														
		X	X	X	X	X		X			X	X	X			X				
Disease Assessment																				
Bone marrow aspirate and/or biopsy¥	X									X							X	Every 2-3 cycle		X
Overall Response Rate‡										X							X		X ‡	X
Study Procedures & Examinations																				
Eligibility Assessment & Informed Consent	X																			
Demographics[A]	X																			
Medical history[B]	X																			
MUGA/ECHO	X																			
Dilated eye exam with fundus photos[N]		X																		
Neurology review and exam[O]		X																		
12-lead ECG (QTcF)	X	X[2]			X[1]			X[1]		X										
Phys. Exam (inc. weight)	X	X			X			X		X	X				X	X	X		X	X
ECOG	X	X									X					X			X	X
Vital Signs (Temp., HR, BP, RR)	X	X[2]	X[3]	X[3]	X[2]	X[1]	X	X[1]		X	X[3]	X[3]	X[1]	X	X	X[3]	X		X	X
Concomitant Medication[C]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Adverse Events[D]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Labs																				
Pregnancy test	X																			
Blood Hematology[E, I, J]	X	X[1]			X[3]	X[3]	X	X[3]	X	X	X			X	X	X	X		X	X
Chemistry[F, I]	X	X[1]			X[3]	X[3]	X	X[3]	X	X	X	X[3]	X[3]	X	X	X	X		X	X
Coagulation, lipase, amylase & urinalysis[G, I]	X	X[1]			X[3]	X[3]	X	X[3]	X	X	X	X[3]	X[3]	X	X				X	X
Lactate and blood pH [I, K]	X	X[1]	X[3]	X[3]	X[1]	X[1]	X	X[1]	X	X	X[3]	X[3]	X[1]	X	X	X[3]	X		X	X
Research Labs																				

Blood collection- pharmacodynamics[H]	X	X[1]			X[1]			X[1]		X										X[L]
Research Bone marrow aspirate/or biopsy	X									X										
Pharmacokinetics Blood samples [I,K,M]		X[2]	X[3]	X[3]	X[2]	X[1]	X	X[1]	X	X	X[3]	X[3]	X[2]	X	X	X[3]	X		X	X[L]

Notes and abbreviations provided on following page.

[A] including Date of Birth; sex; height; race; ethnicity

[B] including oncology history, radiation history

[C] name, indication, dose, route, start and end dates

[D] starting or worsening after study drug administration (signs and symptoms occurring prior to the first dose of study medication on Day 1 should be recorded under the subject's Medical History).

[E] complete blood count, differential, platelets

[F] glucose, total protein, albumin, electrolytes [sodium, potassium, chloride, total CO_2], calcium, phosphorus, magnesium, uric acid, bilirubin (total, direct), SGPT (ALT) or SGOT (AST), alkaline phosphatase, creatinine, blood urea nitrogen, CPK

[G] PT, PTT, fibrinogen, INR

[H] Oxygen consumption, metabolites, protein, mRNA analysis

[I] To be performed weekly during the first cycle of the increased dose for any intra-subject dose escalation

[J] For purposes of data collection, test results below the limit of quantitation will be reported as "0"

[K] If the Investigator determines that the dose of study drug should be interrupted, additional PK, lactate and blood pH assessments will be collected pre-dose (within 2 hours of dosing) and 4 hours +/- 30 minutes post study drug administration upon resumption of dosing; additional PK assessments may be performed during the interruption at the description of the Investigator. If the dose of study drug is reduced, additional PK assessments will be collected pre-dose (within 2 hours of dosing) prior to starting the reduced study drug dose. Additional unscheduled PK, lactate and pH blood draws may be collected per PI judgement when indicated for further safety follow-up.

[L] Additional PK and/or PD draws from peripheral blood may be obtained ~every 4 days, when possible, for up to 4 weeks after last study drug administration in subjects who discontinue the study.

[M] In addition to the time points indicated in the Table, additional draws from peripheral blood for PK analysis may be obtained at the discretion of the Investigator.

[N] Baseline dilated eye exam with fundus photos, including distance acuity (visual acuity charts using refraction-based visual acuity measurement), ophthalmoscopy and slit lamp exam, may be performed up to 14 days prior to study drug administration.

[O] Baseline neurology review and exam to be performed by consultant neurologist up to 14 days prior to study drug administration. The baseline neurology exam may include, but is not limited to, gait and station, cerebellar functions (coordination), upper and lower extremity reflexes, upper and lower muscle strength and sensation.

[1] collected pre-dose (same calendar day of dosing) and 4 hours +/- 30 minutes post study drug administration

[2] collected pre-dose (same calendar day of dosing) and 2, 4, 6, 8 hours (+/- 30 mins) post study drug administration. Note: vitals may be collected (+/- 60 mins) post study drug administration.

[3] collected pre-dose (same calendar day of dosing)

* Treatment will be administered as an inpatient for 24 hours on Day 7 of Cycle 1.
+ Subjects enrolled in the Food Effect group will consume a high fat meal within 30 minutes prior to study drug administration on Day 1 blood sample collection.
§ Study drug will be administered without food, at least 1 hour before and at least 2 hours after eating, with the exception of Day 1 of Cycle 1 for subjects enrolled in the Food Effect group. Induction or maintenance doses and alternative duration of induction doses or other maintenance schedules of IACS-010759, not to exceed 6 mg, may be pursued depending on the safety and PK/PD data observed.
¥ Bone marrow aspirate/biopsy will be performed as clinically indicated, at least once every 3 cycles.
‡ Overall Response Rate (ORR) assessment will be performed on the same schedule as bone marrow aspirate/biopsy (every 2-3 cycles during additional cycles). ORR definitions are provided in Section 5.2.2.

Cohorts 5-6 Dose-Escalation and Cohort 7 Dose-Expansion

	Screen	Cycle 1 (21 days)									Cycle 2 (21 days)					Cycle 3 (21 days)		Additional Cycles (21 days)		End of Study or Early Termination
Study Day	-7 to -1	1+	2	4	5*	8	12	15	17	21	22	29	36	37	42	43	63	Every 21 days		30 after last Dose
Name of Cycle Day		C1 D1	C1 D2	C1 D4	C1 D5	C1 D8	C1 D12	C1 D15	C1 D17	C1 D21	C2 D1	C2 D8	C2 D15	C2 D16	C2 D21	C3 D1	C3 D21	CX D20	CX D21	51
+/- days allowable				1			1	1	2	+2	1	1	1	2	1	3	3	4	4	7
Study Drug§		INDUCTION[P]					MAINTENANCE[P]													
Disease Assessment																				
Bone marrow aspirate and/or biopsy¥	X									X							X	Every 2-3 cycle		X
Overall Response Rate‡										X							X		X ‡	X
Study Procedures & Examinations																				
Eligibility Assessment & Informed Consent	X																			
Demographics[A]	X																			
Medical history[B]	X																			
MUGA/ECHO	X																			
Dilated eye exam with fundus photos[N]		X																		
Neurology review and exam[O]		X																		
12-lead ECG (QTcF)	X	X[2]			X[1]			X[1]		X										
Phys. Exam (inc. weight)	X	X			X			X		X	X				X	X	X		X	X
ECOG	X	X									X					X			X	X
Vital Signs (Temp., HR, BP, RR)	X	X[2]	X[3]	X[3]	X[2]	X[1]	X	X[1]		X	X[3]	X[3]	X[1]	X	X	X[3]	X		X	X
Concomitant Medication[C]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Adverse Events[D]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Labs																				
Pregnancy test	X																			
Blood Hematology[E, I, J]	X	X[1]			X[3]	X[3]	X	X[3]	X	X	X			X	X	X	X		X	X
Chemistry[F, I]	X	X[1]			X[3]	X[3]	X	X[3]	X	X	X	X[3]	X[3]	X	X	X	X		X	X
Coagulation, lipase, amylase & urinalysis[G, I]	X	X[1]			X[3]	X[3]	X	X[3]	X	X	X	X[3]	X[3]	X	X				X	X
Lactate and blood pH [I, K]	X	X[1]	X[3]	X[3]	X[1]	X[1]	X	X[1]	X	X	X[3]	X[3]	X[1]	X	X	X[3]	X		X	X
Research Labs																				
Blood collection- pharmacodynamics[H]	X	X[1]			X[1]			X[1]		X										X[L]

Research Bone marrow aspirate/or biopsy	X									X										
Pharmacokinetics Blood samples [I,K,M]		X[2]	X[3]	X[3]	X[4]	X[1]	X	X[1]	X	X	X[3]	X[3]	X[2]	X	X	X[3]	X		X	X[L]

Notes and Abbreviations:

[A] including Date of Birth; sex; height; race; ethnicity

[B] including oncology history, radiation history

[C] name, indication, dose, route, start and end dates

[D] starting or worsening after study drug administration (signs and symptoms occurring prior to the first dose of study medication on Day 1 should be recorded under the subject's Medical History).

[E] complete blood count, differential, platelets

[F] glucose, total protein, albumin, electrolytes [sodium, potassium, chloride, total CO_2], calcium, phosphorus, magnesium, uric acid, bilirubin (total, direct), SGPT (ALT) or SGOT (AST), alkaline phosphatase, creatinine, blood urea nitrogen, CPK

[G] PT, PTT, fibrinogen, INR

[H] Oxygen consumption, metabolites, protein, mRNA analysis

[I] To be performed weekly during the first cycle of the increased dose for any intra-subject dose escalation

[J] For purposes of data collection, test results below the limit of quantitation will be reported as "0"

[K] If the Investigator determines that the dose of study drug should be interrupted, additional PK, lactate and blood pH assessments will be collected pre-dose (within 2 hours of dosing) and 4 hours +/- 30 minutes post study drug administration upon resumption of dosing; additional PK assessments may be performed during the interruption at the description of the Investigator. If the dose of study drug is reduced, additional PK assessments will be collected pre-dose (within 2 hours of dosing) prior to starting the reduced study drug dose. Additional unscheduled PK, lactate and pH blood draws may be collected per PI judgement when indicated for further safety follow-up.

[L] Additional PK and/or PD draws from peripheral blood may be obtained ~every 4 days, when possible, for up to 4 weeks after last study drug administration in subjects who discontinue the study.

[M] In addition to the time points indicated in the Table, additional draws from peripheral blood for PK analysis may be obtained at the discretion of the Investigator.

[N] Baseline dilated eye exam with fundus photos, including distance acuity (visual acuity charts using refraction-based visual acuity measurement), ophthalmoscopy and slit lamp exam, may be performed up to 14 days prior to study drug administration.

[O] Baseline neurology review and exam to be performed by consultant neurologist up to 14 days prior to study drug administration. The baseline neurology exam may include, but is not limited to, gait and station, cerebellar functions (coordination), upper and lower extremity reflexes, upper and lower muscle strength and sensation.

[P] The dose regimen for the induction and maintenance doses are provided in Table 2.

[1] collected pre-dose (same calendar day of dosing) and 4 hours +/- 30 minutes post study drug administration

[2] collected pre-dose (same calendar day of dosing) and 2, 4, 6, 8 hours (+/- 30 mins) post study drug administration. Note: vitals may be collected (+/- 60 mins) post study drug administration.

[3] collected pre-dose (same calendar day of dosing)

[4] collected pre-dose (same calendar day of dosing) and 2, 4, 6, 8 hours (+/- 30 mins) and 24 hours (+/- 2 hours) post study drug administration. Note: vitals may be collected (+/- 60 mins) post study drug administration.

* Treatment will be administered as an inpatient for 24 hours on Day 5 of Cycle 1.
+ Subjects enrolled in the Food Effect group will consume a high fat meal within 30 minutes prior to study drug administration on Day 1 blood sample collection.
§ Study drug will be administered without food, at least 1 hour before and at least 2 hours after eating, with the exception of Day 1 of Cycle 1 for subjects enrolled in the Food Effect group. Induction or maintenance doses and alternative duration of induction doses or other maintenance schedules of IACS-010759, not to exceed 6 mg, may be pursued depending on the safety and PK/PD data observed.
¥ Bone marrow aspirate/biopsy will be performed as clinically indicated, at least once every 3 cycles.
‡ Overall Response Rate (ORR) assessment will be performed on the same schedule as bone marrow aspirate/biopsy (every 2-3 cycles during additional cycles). ORR definitions are provided in Section 5.2.2.

Study Objectives & Endpoints

Primary Objectives	Safety & Tolerability Determine Dose Limiting Toxicities Establish MTD and RP2D
Secondary Objectives	IACS-010759 pharmacokinetics and food effect Preliminary Clinical Efficacy (overall response rates, duration of response, progression-free survival, overall survival)
Exploratory objectives	Pharmacodynamic and exploratory biomarkers of activity of IACS-010759

Clinical study data will be entered into Medidata Rave, the clinical data base, via electronic case report forms. The Statistical Analysis Plan (SAP) will include detailed and specific description of all analysis to be performed on the clinical data from this study. The SAP will be finalized prior to database lock.

All statistical analyses will be performed using Version 9.4 or later of Statistical Analysis Software (SAS®). Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], Q1, median, Q3, minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage. All data collected will be included in by-subject data listings.

Unless otherwise specified, all tests will be two-tailed using a 0.05 level of significance. All confidence intervals (CIs) will be two-sided 95% confidence intervals.

All subjects who received any study drug and who had any on-treatment evaluation will be included in the Full Analysis Set (FAS).

4.3 Safety and tolerability

4.3.1 Endpoints & Assessment Methods

Laboratory tests, vital sign measurements, physical exams and subject interviews will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. All "treatment-emergent" clinically significant abnormalities and deteriorations that begin or worsen in severity after initial administration of IACS-010759 and documented as such in the medical records should be recorded in the Case Report Forms as Adverse Events and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

The MTD will be determined in accordance with Section 4.1.7.

4.3.2 Subject Evaluation & Statistics

The FAS will be used for evaluation of safety.

Adverse events will be coded using the MedDRA dictionary. Incidences of treatment-emergent adverse events (TEAE, those events that started after dosing or worsened in severity after dosing) will be presented overall and by maximum severity (according to CTCAE Ver 4.03) and relationship to study medication.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented by cohort for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. Additionally, for each continuous hematology and chemistry parameter, descriptive statistics will be presented by cohort for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented by cohort for the changes in vital signs from baseline to each post-treatment assessment time point.

4.4 Clinical Efficacy

4.4.1 Subject Evaluation & Statistics

The FAS will be the basis for the evaluation of clinical efficacy.

Disease assessment will be performed at the end of Cycles 1, 3, and thereafter every 2-3 cycles at the discretion of the treating physician. While the bone marrow aspirate/biopsy will be performed as clinically indicated, testing will occur at least once every 3 cycles.

Descriptive statistics will be provided for continuous variables and frequency tables will be used to summarize categorical variables. The Overall Response Rate and the proportions of subjects who experienced CR, Cri, PR, MLFS (morphologic leukemia-free state), hematologic improvements, Recurrence of Disease (RD) and Best Response measurement along with the corresponding exact 95% confidence intervals will be displayed.

Kaplan-Meier method will be used to estimate the duration of response, progression-free survival and overall survival. These time to event variables will be summarized using the 25^{th} percentile, Median, and 75^{th} percentile as well as the minimum and maximum time to event, calculated by Kaplan-Meier method, and will be displayed graphically.

4.4.2 Endpoints & Assessment Methods

Objective Overall Response Rate (ORR) for subjects with AML include CR, CRi, PR and morphologic leukemia-free state [22] with or without cytogenetic response and hematologic improvements. The responses are defined as below:

- **Complete Remission (CR)**
  For subjects to be classified as being in CR, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an ANC > 1×10^9/L and platelet count ≥ 100×10^9/L, and normal marrow differential with < 5% blasts, and subjects will be red blood cell (RBC) and platelet transfusion independent (defined as 4 weeks without RBC transfusion and 1 week without platelet transfusion). There should be no evidence of extramedullary leukemia.
- **Complete Remission with Incomplete Hematological Recovery (CRi)**
  For subjects to be classified as being in CRi, they must fulfill the criteria for CR except for incomplete hematological recovery with residual neutropenia (ANC ≤ 1×10^9/L) with or without thrombocytopenia (platelet count < 100×10^9/L). In addition, subjects do not need to be RBC or platelet transfusion independent (modification to Cheson criteria).
- **Partial Remission (PR)**
  For subjects to be classified as being in PR, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few

regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5% and 25%.

- **Morphologic leukemia-free state (MLFS)**:
  Bone marrow: ≤5% myeloblasts
- **Hematologic Improvement (HI):**
  Hematologic response must be described by the number of positively affected cell lines.
  - Erythroid response (E) (pretreatment Hgb <11 g/dL)
  - Hgb increase by ≥1.5 g/dL
  - Platelet response (P) (pretreatment platelets <100 x10^9/L)
  - Absolute increase of ≥30 x 10^9/L for subjects starting with > 20 x 10^9/L platelets
  - Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
  - Neutrophil response (N) (pretreatment ANC <1.0 x10^9/L)
  - At least 100% increase and an absolute increase > 0.5 x 10^9/L
  - Blast response (B)≥50% reduction in peripheral blood or bone marrow blasts but still >5%
- **Recurrence of Disease (RD)**
  Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukemia. Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to > 25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.
- **Best Response measurement:** Response will be measured and defined for primary endpoints as the best response achieved during the first 3 cycles of therapy, or at time off study, for those subjects discontinuing treatment before the completion of 3 cycles of therapy. Best response is defined to be the best-measured response (ORR=CR+CRp+PR+MLFS) post-treatment up to that time. Best response will also be evaluated for the full treatment period using all assessments up to and including treatment discontinuation.

Duration of Response: length of time from the first objective evidence of response to the first objective evidence of disease progression.

Progression-Free Survival: length of time (up to 5 years) from the date of first treatment to the first objective evidence of disease progression or death, whichever is earlier.

Overall Survival: length of time from the date of first administration of study drug to the date of death from any cause.

4.5 IACS-010759 Plasma Drug Levels

4.5.1 Subject Evaluation & Statistics

Only subjects who received at least one dose of IACS-010759, and provided both the baseline sample and at least one post-treatment sample, will be evaluated.

4.5.2 Endpoints & Assessment Methods

Collection of samples to assess the plasma concentration of IACS-010759 will be required for all subjects. Peripheral blood (5 mL) will be collected at the time points indicated in section 4.2.

A validated LC-MS/MS bioanalytical method will be used at the MDACC, Institute for Applied Cancer Science (IACS) research labs, located at 4SCRB2.1175, 1901 East Road, Houston, TX to quantify IACS-010759 in human plasma.

Pharmacokinetic parameters will be calculated using Phoenix WinNonlin 6.3 software package.

4.6 Biological activity of IACS-010759

4.6.1 Subject Evaluation & Statistics

Only subjects who received at least one dose of IACS-010759, and provided the baseline and at least one post-treatment sample, will be evaluated.
PD data will be summarized graphically and with descriptive statistics by time and dose.

4.6.2 Endpoints & Assessment Methods

To evaluate PD biomarkers, approximately 30 cc of peripheral blood will be collected in green top tubes and 5 cc of bone marrow will be collected at the time points indicated in section 4.2. Upon isolation of blasts cells, baseline and post-treatment biological activity will be assessed using assays that are informed by preclinical studies using AML cell line and subject derived models. These include but are not limited to:

- Pre and post-treatment measurement of OXPHOS inhibition, using Seahorse Seahorse XF bioanalyzer to measure oxygen consumption in blast cells isolated from the peripheral blood.
- Pre and post-treatment measurement of metabolites related to mitochondria metabolism, glycolysis, amino acid and nucleotide biosynthesis, to measure changes that have been associated with inhibition of OXPHOS and response in preclinical models.
- Pre and post treatment measurement of mRNAs using gene expression profiling or other quantitative methods to assess mRNA signatures that has been identified utilizing preclinical models treated with IACS-010759.

Any leftover sample or tissue including bone marrow, if available, will be stored for potential future exploratory research into factors that may influence development of AML and/or response to IACS-010759 (where response is defined broadly to include efficacy, tolerability or safety) or additional exploratory pharmacogenetic evaluations, including RNA microarray analyses or DNA, and xenografting into immunodeficient mice. Excess samples will be stored at MD Anderson Cancer Center, IACS laboratory, located at 4SCR6.1100, 1901 East Road, Houston, TX.

5 Subject Eligibility

5.1 Inclusion Criteria

*Eligible subjects **must fulfill** all of the following criteria:*

1.	Subjects with AML should have failed any prior induction therapy regimen or have relapsed after prior therapy (defined as patients in first relapse and less than 12 months from diagnosis [short first remission] or in second or later relapse

	Dose-escalation phase: Subjects with confirmed relapsed or refractory AML and no available treatment options with known benefit Expansion phase: Subjects with relapsed/refractory AML who have failed therapy with up to one prior salvage regimen and no available treatment options with known benefit Exception: stem cell transplant [SCT] or stem cell therapy for subjects who previously underwent SCT/stem cell therapy, and are currently in remission will not be considered a salvage regimen.
2.	Eastern Cooperative Oncology Group (ECOG) ≤ 2 (see appendix 9.3)
3.	Patients who have had prior SCT are eligible if they have a relapse > 3 months since autologous or allogeneic stem cell transplantation provided, • No clinically significant active graft-versus-host disease (GVHD > grade 1). • No treatment with high dose steroids for GVHD (i.e. >20 mg Prednisolone or equivalent per day). • No treatment with immunosuppressive drugs with the exception of cyclosporine and tacrolimus.
4.	Subjects with history of CNS disease are allowed if at the time of day 1 of the study there is no evidence of active CNS disease as documented by negative imaging or spinal fluid analysis carried out at least 2 weeks prior to the first study drug administration in a subject with no clinical signs of CNS disease.
5.	Adequate renal and hepatic function: • Serum creatinine ≤ 2.0 X ULN • Total bilirubin ≤ 2 times the upper limit of normal (ULN) (or </= 3.0 x ULN if deemed to be elevated due to Gilbert's disease or leukemia) • ALT and AST ≤ 2.5 times ULN (≤ 5.0 x ULN if due to leukemic involvement).
6.	Negative urine pregnancy test within 72 hours prior to the first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post- menopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months).
7.	Have been informed of other treatment options and is not a candidate for standard treatment options or stem cell transplant at the time of enrollment.
8.	Age ≥18 years.
9.	In the absence of rapidly progressing disease, the interval from prior treatment to time of initiation of IACS-010759 administration will be at least 2 weeks or 5 half-lives (whichever is shorter) for cytotoxic/noncytotoxic agents and biological/immune-based therapies, including investigational agents. The half-life for the therapy in question will be based on published pharmacokinetic literature (abstracts, manuscripts, investigator brochures, or drug-administration manuals) and will be documented in the protocol eligibility document. The use of chemotherapeutic or anti-leukemic agents is not permitted during the study with the following exceptions: (1) intrathecal (IT) therapy for subjects with controlled CNS leukemia at the discretion of the PI and with the agreement of the Sponsor. (2) Use of hydroxyurea for subjects with rapidly proliferative disease is allowed before the start of study therapy and for the first 2 cycles on therapy. These medications will be recorded in the case-report form.

10.	Women of childbearing potential must agree to use an adequate method of contraception during the study and until 3 months after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment. Adequate methods of contraception include: • Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment • Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject • Combination of any of the two following (a+b or a+c or b+c) a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception b. Placement of an intrauterine device (IUD) or intrauterine system (IUS) c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository In case of use of oral contraception, women should have been stable on the same pill before taking study treatment. **Note:** Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
11.	Able and willing to give valid written informed consent.

5.2 Exclusion Criteria

*Subjects **may not** enter the study if they fulfill any of the following criteria:*

1.	Prior exposure to IACS-010759 or other oxidative phosphorylation Inhibitors.
2.	Unstable cardiovascular function: • Symptomatic ischemia, or • Uncontrolled clinically significant conduction abnormalities (i.e., ventricular tachycardia on antiarrhythmic agents are excluded; 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or • Congestive heart failure (CHF) NYHA Class ≥ 3 (Appendix 9.5), or • Myocardial infarction (MI) within 6 months. • Left ventricular ejection fraction < 40 %. • Hypertension > 160 mm Hg systolic or > 100 mm Hg diastolic with or without antihypertensive therapy.
3.	Major surgery, other than diagnostic surgery, within 4 weeks prior to Day 1, without complete recovery from the surgical procedure
4.	Presence of ≥ CTCAE grade 2 toxicity (except alopecia or peripheral neuropathy) due to prior cancer therapy.
5.	Known positive for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg), or hepatitis C virus (HCV).
6.	Active uncontrolled infection. Infections controlled on concurrent anti-microbial agents are acceptable, and anti-microbial prophylaxis per institutional guidelines is acceptable.
7.	Participation in any other clinical trial involving another investigational agent for the treatment of AML within 2 weeks prior to day 1 of the study or at least 5 half-lives of the investigational agent, whichever is shorter.
8.	Lactate levels > 2 mmol/L and or and serum pH <7.35 at screening.
9.	Subject currently being treated with biguanides or other agents known to increase risk of lactic acidosis (reference Appendix 10.1).
10.	Subject has significant gastrointestinal abnormalities, including ulcerative colitis, chronic diarrhea associated with intestinal malabsorption, Crohn's disease, and/or prior surgical procedures affecting absorption or requirement for intravenous (IV) alimentation.
11.	Subjects with uncontrolled Type I or II diabetes mellitus
12.	Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study.
13.	Women who are breast-feeding or pregnant as evidenced by positive urine pregnancy test done within 72 hours of first dosing.
14.	Subject has a concurrent active malignancy under treatment, with the exception of: -Adequately treated carcinoma in situ of the breast or cervix uteri -Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin -Low-grade, early-stage prostate cancer with no requirement for therapy -Previous malignancy confined
15.	Acute promyelocytic leukemia.

16.	Any concomitant disease or condition that, in the clinical judgment of the treating physician, is likely to prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.
17.	Subjects with ≥ grade 1 peripheral neuropathy at screening.

6 Study Drug

6.1 Study Drug Administration

Cohorts 1 and 2: For each cycle 1, a single oral dose of IACS-010759 will be administered on day 1. The next dose of IAC-010759 will be administered on day 8, and daily continuously for the duration of the study with no interruptions unless there are adverse events as described in Section 4.1.9. IACS-010759 doses will be separated by intervals of approximately 24 hours (+/- 3 hours).

Cohorts 3-6 and Dose Expansion: Based on the observed accumulation of IACS-010759 throughout the dosing period in cohorts 1 and 2, a modified dosing regimen is being implemented, consisting of an induction phase in which IACS-010759 is administered daily for up to 7 days, followed by a maintenance phase in which a lower dose is administered weekly (or as otherwise specified by the SMC based on safety, PK and PD data observed) to maintain steady state plasma levels. Dosing will proceed on this schedule for the duration of the study with no interruptions unless there are adverse events as described in Section 4.1.9.

IACS-010759 will be administered without food, at least 1 hour before and at least 2 hours after eating. Each dose of IACS-010759 should be administered with 8 ounces of water. If a dose is missed, the next dose will not be increased to account for missing a dose. The subject will take the next regular dose at the scheduled time. Following cycle 1 (28-day cycle for cohorts 1 and 2, 21 day cycle for subsequent cohorts), subjects will receive one cycle of therapy every 21 days (+/- 4 days).

In cohorts 1 and 2, treatment was administered as an inpatient for 24 hours on day 1 and then starting on day 8 for the next 7 days for all enrolled subjects. In cohorts 3 and 4, treatment will be administered as an inpatient for 24 hours on Day 7 of Cycle 1 for all enrolled subjects. In subsequent cohorts, treatment will be administered as an inpatient for 24 hours on Day 5 of Cycle 1 for all enrolled subjects. IACS-010759 will be self-administered and subjects instructed not to dose on days when PK/PD samples are collected until advised by the research staff. Self-administration can occur on days without PK/PD and subjects will record administration in a provided diary.

In the expansion phase, after the first 6 subjects have been enrolled in the expansion cohort, the next 6 subjects will be enrolled in the Food Effect group where the effect of a high fat meal on the PK of IACS-010759 will be evaluated on day 1 of cycle 1 for the cohort (Food Effect group). The dose level to be administered will be the single agent RP2D induction dose as determined in the escalation phase or may be lower than the RP2D if clinical safety concerns prevent the use of RP2D for the food effect evaluation. Subjects in the Food Effect group will consume the high-fat meal within 30 minutes *prior to* IACS-010759 administration and blood samples collected at

the timepoints listed in the Study Flowchart for PK analysis. After this day 1 dose, subsequent doses of IACS-010759 will be administered without food as described above for the remainder of the cycle. The plasma levels in these subjects will be compared to those of the other subjects in the expansion cohort to determine whether consumption of a meal affects the plasma levels of IACS-010759.

6.2 Study Drug Information

MDACC, IACS has defined a chemical synthesis process, specific purity profile and release specifications for the manufacture of IACS-010759. WuXi AppTec Co, Ltd. is producing GMP material on a 2.5 kg scale. The final drug product will be a dry filled capsule (DFC) formulation for oral administration.

Study drug will be packaged in 28-count bottles of 4 strengths: 0.1 mg, 0.5 mg, 1.0 mg and 5.0 mg, as described in Table 6. The first dose strength to be administered in cohort 1 of the dose escalation phase is 0.5 mg. Study drug may be stored at room temperature.

Table 6: IACS-010759 Drug Product Appearance by Strength

Strength	Appearance
0.1 mg	Hard Gelatin capsules, Size 3, white opaque cap, white opaque body
0.5 mg	Hard Gelatin capsules, Size 3, light green opaque cap, white opaque body
1.0 mg	Hard Gelatin capsules, Size 3, light blue opaque cap, white opaque body
5.0 mg	Hard Gelatin capsules, Size 3, dark blue opaque cap, white opaque body

The active ingredient in IACS-010579 is manufactured under GMP conditions by:
Shanghai SynTheAll Pharmaceutical Co. Ltd.,
9 Yuegong Road,
Jinshan District,
Shanghai 201507, China

The finished drug product is manufactured under GMP conditions by:
WuXi AppTec Co., Ltd,
299 FuTe Zhong Road,
Waigaoqao Free Trade Zone,
Shanghai, 200131, P. R. China

6.3 Drug Overdose Management

There are no known antidotes available for the IACS-010759. Any overdoses with this drug should be managed symptomatically.

7 Concurrent and Supportive Therapies

7.1 Non-Permitted Concomitant Therapies

*Subject **may not** receive the following concomitant therapies during the study:*

1.	Biguanides or other agents known to increase risk of lactic acidosis (Appendix 10.1)
2.	High dose steroids (>20 mg prednisolone or equivalent per day) including for GVHD
3.	Immunosuppressive drugs with the exception of cyclosporine and tacrolimus
4.	Erythropoietin and growth factors are not permitted to be used prophylactically in cycle 1 but allowed if needed in cycle 2 and onwards. However, these can be used therapeutically throughout the study.
5.	Other cancer therapy (chemotherapy, radiation or immunotherapy) other than the exceptions mentioned in Inclusion Criteria #9.
6.	Strong cytochrome P450 (CYP450) inhibitors or inducers, as specified below:

CYP Enzyme	Strong Inhibitors	Strong Inducers
CYP1A2	Ciprofloxacin, clinafloxacin, enoxacin, fluvoxamine, zafirlukast	
CYP2C8	Gemfibrozil	
CYP2C19	Fluconazole, fluvoxamine, ticlopidine	
CYP3A	Clarithromycin, conivaptan, grapefruit juice, itraconazole, ketoconazole, mibefradil, nefazodone, posaconazole, telithromycin, troleandomycin, voriconazole	Avasimibe, carbamazepine, phenobarbital, phenytoin, pioglitazone, rifbatun, rifampin, St. John's wort
CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	

7.2 Supportive Care Guidelines & Permitted Concomitant Therapies

7.2.1 Concomitant medication/therapies

In general, the use of any concomitant medication/therapies deemed necessary for subject supportive care and safety are permitted. Subjects with high WBC counts may receive hydroxyurea prior to study entry and during the first 2 cycles. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted as defined in the inclusion criteria. With the exception of these agents, concomitant systemic chemotherapy is not permitted.

Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are allowed for managing myelosuppression as shown in the table below. Concomitant medications will be recorded in the Case Report Form.

Table 8: Instructions for the use of concomitant medications and therapies

Category of Use	Medication	Comment on Use	Restriction on Use
Recommended	Prophylactic antibiotics, antifungal agents, and antiviral agents.	Strongly encouraged	Agents known to increase risk of lactic acidosis (see Appendix 10.1)
	Antiemetic agents	According to standard of care at MDACC	None
Allowed	Oral allopurinol or rasburicase	At investigators discretion	None
	Leukapheresis	According to standard of care at MDACC	Before induction 1 day 1 only
	Red blood cell transfusion	None	None
	Platelet transfusion	None	None
	White blood cell transfusion	At investigators discretion according to standard of care at MDACC	None
	Myeloid growth factors or platelet growth factor	At investigators discretion according to standard of care at MDACC	None
	Erythropoietin or darbepoetin	At investigators discretion according to the standard of care at MDACC	None
	Any other medication for supportive care	At investigators discretion according to standard of care at MDACC	Agents known to increase risk of lactic acidosis (see Appendix 10.1)

7.2.2 Use of Blood Products

During the administration of IACS, subjects may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines.

Myelosuppression is expected in subjects with AML due to underlying disease. Most subjects will have neutropenia, thrombocytopenia, or both at study entry. Significant or life-threatening myelosuppression may be managed with growth factor support including G-CSF, GM-CSF and platelet growth factors and erythropoietin/darbopoietin/blood transfusion according to institutional standard of care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and/or NCCN Practice Guidelines.

7.2.3 Lactic Acidosis and Severe Acidemia Management

Subjects with lactic acidosis and severe acidemia (pH < 7.1) should be seen by a nephrology specialist as soon as possible and receive bicarbonate therapy. When using bicarbonate therapy in subjects with lactic acidosis and severe acidemia, the aim is to maintain the arterial pH above 7.1. Rapid infusions of sodium bicarbonate may increase the pCO_2, accelerate the production of lactate, lower the ionized calcium, expand the extracellular space, and raise the serum sodium concentration. There is little evidence that any alternative buffering agents are superior to bicarbonate therapy. In adequately ventilated subjects with lactic acidosis and severe acidemia, 1 to 2 mEq/kg sodium bicarbonate is given as an intravenous bolus. This dose is repeated after 30 to 60 minutes if the pH is still below 7.1.

8 Administrative, Legal & Ethical Requirements

8.1 Adverse Event, serious adverse event and reporting

8.1.1 Adverse Event (AE):

Any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product.

The criteria for identifying AEs are:

- 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
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of laboratory value or other clinical test (e.g., ECG or X-ray) that results in symptoms, a change in treatment, or discontinuation from study drug
- Recurrence of an intermittent medical condition (e.g. headache) not present at Baseline.

An abnormal laboratory test result may be considered as an adverse event if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A laboratory result should be considered by the Investigator to be an adverse event if it:

- Results in the withdrawal of study treatment
- Results in withholding of study treatment pending some investigational outcome
- Medical evaluation, results in the initiation of an intervention (e.g. potassium supplement for hypokalemia)
- Any out of range laboratory value that in the Investigator's judgment, fulfills the definitions of an AE with regards to subject's medical profile
- Increases in severity compared to Baseline by ≥ 2 NCI grades (see Appendix C for NCI CTCAE Ver 4.03 criteria), with the exception of lymphocytes, albumin, cholesterol, glucose and phosphate. For these tests, a change of ≥ 2 grades will be evaluated by the Investigator to determine if they are of clinical significance and if so, will be considered an adverse event.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an adverse event should be reported on the Adverse Event Case Report Form (CRF).

It is the responsibility of the Investigator to review all laboratory findings, including laboratory assessments performed at outside labs, in all subjects and determine if they constitute an adverse event. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. The Investigator will assess external laboratory findings and determine clinical significance of any which are deemed adverse events. In these instances, the laboratory reports should be signed and dated by the Investigator.

8.1.2 Reporting of Adverse Events

Adverse events will be recorded by the research personnel on the CRF. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

For this protocol, adverse events and protocol specific data will be entered into the electronic case report form. Serious adverse events will be entered into ARISg and reconciled against the clinical data base at the end of the study. All AEs encountered during the clinical study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected, beginning from the time of the first protocol-specific intervention (study drug administration). New information regarding signs and symptoms that occurred prior to the first study medication dose on Day 1 should be recorded under the subject's Medical History. Adverse events in clinical investigation subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.

Subjects with AEs that are ongoing at the subject's last study visit must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first. Adverse events that are reported during the Follow-up Period will be recorded on the Adverse Events CRF and followed until resolution or for up to the 30 days after the subject's last study visit, whichever comes first, with the exception that SAEs will be followed until the event resolves or the event or sequelae stabilize.

Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study treatment.

8.1.3 Assessing Severity of Adverse Events

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Ver 4.03; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) is used to assign severity scales to AEs.
They are:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Life Threatening
Grade 5 = Death

Elevated lactate levels are an anticipated pharmacodynamic effect of OXPHOS inhibitors. It is currently unknown if such effects may lead to biological consequences, such as lactic acidosis or

associated symptoms. Safety and tolerability of IACS-010759 is the primary objective of this phase 1 clinical trial. During this study, if elevated lactate levels are observed and subjects are hospitalized for observation of signs and symptoms (as described in Section 4.1.11), such hospitalization (or prolongation of hospitalization) for observation of signs and symptoms that would not otherwise require hospitalization will not be considered as a grade 3 toxicity when grading the severity of the adverse event if subjects remain asymptomatic and pH remains normal.

In addition, all AEs reported using the NCI CTCAE Ver 4.03 classification and graded as 4 or 5 are to be considered serious. The recommended Adverse Event Recording Guidelines are provided in Section 8.1.7.

The criteria for assessing severity are different than those used for seriousness.

8.1.4 Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, considering especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment, or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study treatment related factors which are known to be associated with the occurrence of the event

8.1.5 Classification of Causality

Causality is a determination of whether there is a reasonable possibility that the drug may have caused or contributed to an adverse event. It includes assessing temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying diseases, and the presence (or absence) of one or more likely causes.

The investigator must attempt to determine whether an adverse event is in some way related to the use of the study drug. This relationship should be described as follows:

Unlikely: The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, or a new condition that, based on the pathophysiology of the condition and the pharmacology of the study drug, is unlikely to be related to the use of the study drug.

Possible: The event follows a reasonable temporal sequence from administration of the study drug or the event follows a known response pattern to the study drug, *but* the event could have been produced by a concomitant medication or an intercurrent medical condition which, based on the pathophysiology of the condition and the pharmacology of the study drug, is unlikely to be related to the use of the study drug.

Probable: The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug and the event cannot be

reasonably explained by an intercurrent medical condition *or* the event cannot be the effect of a concomitant medication.

Definite: The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug, and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

Unknown: Based on the evidence available, causality cannot be ascribed.

8.1.6 Reporting Requirements

Reporting requirements will be as per institutional guidelines.

Adverse events (AE) related to study conditions

The serious adverse event (SAE) reporting period will begin with the time of the first protocol-specific intervention (study drug administration) Regardless of severity or seriousness, new information regarding signs and symptoms that occurred prior to the first study medication dose on Day 1 should be recorded under the subject's Medical History.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such subjects should receive post-treatment follow-up as appropriate.

8.1.7 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the subject, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Subject hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, to the PROMETRIKA Safety Manager.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the PROMETRIKA Safety Manager, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the PROMETRIKA Safety Project Manager.
- Unless otherwise noted, the entry of an AE that is designated as serious in the EDC system will automatically prompt an automated email alert for a newly entered case or for an existing case where a change in status of the AE fields has been made by the site. The email alert will be sent to relevant personnel involved with the SAE case management, including the PROMETRIKA Safety Manager. In the event that the site is unable to send the information through the EDC, the site will contact the Drug Safety Management department at PROMETRIKA by phone (617.844.0205) or fax (617.868.2122) and forward the SAE Form and other related documents to the PROMETRIKA Safety Manager. The site will be responsible for safety reporting to the MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention (study drug administration), until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, all serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the Sponsor and the PROMETRIKA Safety Manager. This may include the development of a secondary malignancy.

Recommended Adverse Event Recording Guidelines

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.1.8 Reporting to FDA:

PROMETRIKA will submit **all** SAE reports to the IND Office via e-mail to MDACCSafetyReports@mdanderson.org. Serious adverse events will be submitted to FDA by the IND Sponsor (Safety Project Manager, IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

8.1.9 Unexpected Adverse Event

An unexpected adverse event is one that is not listed in the current Clinical Investigator's Brochure (CIB) / Package Insert or that differs from the event mentioned in the CIB / Package Insert because of greater severity or specificity.

9 Appendices

9.1 Causes of elevated lactate

Shock	Pharmacological agents*
Distributive	Linezolid
Cardiogenic	Nucleoside reverse transcriptase inhibitors
Hypovolemic	Metformin
Obstructive	Epinephrine
Post-cardiac arrest	Propofol
Regional tissue ischemia	Acetaminophen
Mesenteric ischemia	$Beta_2$ agonists
Limb ischemia	Theophylline
Burns	
Trauma	Anaerobic muscle activity
Compartment syndrome	Seizures
Necrotizing soft tissue infections	Heavy exercise
Diabetic ketoacidosis	Excessive work of breathing
Drugs/toxins	Thiamine deficiency
Alcohols	Malignancy
Cocaine	Liver failure
Carbon monoxide	Mitochondrial disease
Cyanide	

Adapted from [23]

9.2 List of abbreviations

AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
CBC	Complete Blood Chemistry
CR	Complete Remission
CRi	Complete Remission with Incomplete Hematological Recovery
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-drug interaction
DLT	Dose-limiting Toxicity
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
HI	Hematologic Improvement
IACS	Institute for Applied Cancer Science
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LC-MS	Liquid Chromatography–Mass Spectrometry
LLN	Lower Limit of Normal
LSC	Leukemic Stem Cells
MDACC	MD Anderson Cancer Center
MTD	Maximum Tolerated Dose
MLFS	Morphologic leukemia-free state
NOAEL	No Observed Adverse Effect Level
ORR	Overall Response Rate
OXPHOS	Oxidative Phosphorylation
PD	Pharmacodynamic
PK	Pharmacokinetic
pAMPK	Adenosine Monophosphate Activated Protein Kinase
PI	Principal Investigator
PR	Partial Remission
RD	Recurrence of Disease
RP2D	Recommended Phase 2 Dose
QTcF	Fridericia Correction Formula
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SD	Standard Deviation
ULN	Upper Limit of Normal

9.3 ECOG Performance Status*

Grade	ECOG
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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

9.4 New York Heart Association (NYHA) Functional Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

9.5 References

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