A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, RANDOMIZED STUDY OF PRACINOSTAT IN COMBINATION WITH AZACITIDINE IN PATIENTS ≥18 YEARS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA UNFIT FOR STANDARD INDUCTION CHEMOTHERAPY

PROTOCOL NUMBER:	PRAN-16-52
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PROTOCOL DATE:	16 Dec 2019

The clinical trial will be conducted, and essential study documentation archived, in compliance with this protocol, applicable SOPs and standards, which incorporate the requirements of the ICH Guideline for Good Clinical Practice.

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INVESTIGATOR ACCEPTANCE APPROVAL PAGE

TITLE:	A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, RANDOMIZED STUDY OF PRACINOSTAT IN COMBINATION WITH AZACITIDINE IN PATIENTS ≥ 18 YEARS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA UNFIT FOR STANDARD INDUCTION CHEMOTHERAPY
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SPONSOR:	Helsinn Healthcare SA

I have read and understood the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines and all applicable government regulations and the ICH-GCP.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board (IRB)/Ethics Committee (EC) approval of the Protocol and Informed Consent Form (ICF) prior to enrollment of patients in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC except when such modification is made to remove an immediate hazard to the patient.

I will ensure that a fully executed ICF is obtained from each patient prior to initiation of any study procedures.

I will report any serious adverse event that occurs during the course of the study in accordance with the procedures described in this protocol and in accordance with local and ICH/GCP regulatory requirements.

I will allow the Sponsor, Helsinn Healthcare SA and its designees as well as the United States Food and Drug Administration and other Regulatory Agencies, to inspect study facilities and pertinent records, ensuring patient confidentiality. If I am notified that this study is to be inspected by a Regulatory Agency, I will notify Helsinn Healthcare SA /designee as soon as possible thereafter.

Principal Investigator's Name (print)	Site Number
Principal Investigator's Signature	Date (day/month/year)

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PROTOCOL SYNOPSIS

Title:	A Phase III, Double-Blind, Placebo-Controlled, Multicenter, Randomized Study of Pracinostat in Combination with Azacitidine in Patients ≥18 Years with Newly Diagnosed Acute Myeloid Leukemia (AML) Unfit for Standard Induction Chemotherapy
Protocol Number:	PRAN-16-52 (Original Protocol Number: MEI-009)
EudraCT Number:	2016-004724-34
Test Product:	Pracinostat
Phase:	III
Indication:	Acute Myeloid Leukemia (AML)
Study Sites:	Approximately 130 worldwide
No. of Patients:	Up to 500
Study Design	This is a Phase III, multicenter, double-blind, randomized study of pracinostat vs. placebo with azacitidine (AZA) as background therapy in patients ≥ 18 years of age with newly diagnosed acute myeloid leukemia (AML), excluding acute promyelocytic leukemia and cytogenetic low-risk AML, who are unfit to receive intensive remission induction chemotherapy due to age ≥ 75 years or comorbidities. Patients will be randomized in a 1:1 ratio to one of two groups: Group A (experimental group) to receive pracinostat plus AZA and Group B (control group) to receive placebo plus AZA. Randomization will be stratified by cytogenetic risk category (intermediate vs. unfavorable risk, according to SWOG Cytogenetic Risk Category Definitions, Appendix B) and ECOG performance status (0-1 vs. 2, Appendix C). Treatment will be administered based on 28-day cycles, with pracinostat/placebo administered orally once every other day, 3 times a week for 3 weeks, followed by one week of no treatment and AZA administered for 7 days of each cycle. Study treatment should continue until there is documented disease progression, relapse from complete remission (CR), or non-manageable toxicity. A minimum of 6 cycles may be required to achieve a complete remission. Once permanently discontinued from study treatment, patients will enter the Long-term Follow-up phase of the study and will be followed for assessment of disease progression, if applicable, and survival every 3 months (±1 month) until death. The end of this study is defined when 390 events (deaths) have occurred. Patients who are receiving study treatment at the end of the study may have the opportunity to continue to receive the study drug to which they were

	randomized to (Post-Study Observation Period), until the Sponsor informs the Investigators of the appropriate course of action, based on the study results. The Post-Study Observation Period is defined as the period starting from the end of the study for a maximum of 24 months.
Background and Study Rationale	Approximately about 21,380 new cases and 10,590 deaths from AML are expected to occur in the United States (US) in 2017, with the disease most commonly diagnosed in older people [American Cancer Society, 2017]. The average age of patients with AML is 67 years [American Cancer Society, 2017]. According to the Surveillance of Rare Cancers in Europe (RARECARE) project, the incidence of AML in Europe is 3.7 per 100,000 [Visser, 2012], similar to an incidence of 4.1 per 100,000 in the US [SEER, 2016]. Population-based studies have reported 3-year survival rates of 9-10% in patients ≥ 60 years of age, compared with 5-year survival rates of up to 50% for patients < 60 years [Luger, 2010]. Poor overall survival (OS) in elderly patients with AML is due to two main factors: 1) high-risk disease characteristics (e.g., secondary AML, poor cytogenetic features) that respond poorly to standard induction chemotherapy, and 2) co-morbidities that preclude the use of intensive (curative) chemotherapy regimens. In addition, a much smaller but not trivial proportion of younger patients with AML are not able to receive standard induction chemotherapy due to comorbidities. Common approaches for patients with AML unfit to receive standard induction therapy regimens consist of low intensity therapies such as hypomethylating agents (HMA), low dose cytarabine, cloforabine, or supportive care measures, but their benefit is limited. New treatment approaches are needed. Pracinostat, a potent, oral, pan-Histone DeACetylase (HDAC) (including Class I, II, and IV isoforms) inhibitor with favorable pharmacokinetic (PK) properties, has been administered to more than 400 patients with solid tumors or hematologic cancers in multiple Phase I and Phase II clinical studies, and has shown efficacy in myeloid malignancies. A Phase II, open-label, single-arm, multicenter study evaluated pracinostat in combination with AZA in 50 patients aged ≥ 65 years with newly diagnosed AML not eligible for induction chemotherapy (Study MEI-004). The primary objective was to estimate the composite complete remission (cCR) rate, composed of morphologic complete remission (CR) + morphologic complete remission with incomplete blood count recovery (CRi) + morphologic leukemia free state (MLFS). The CR rate was 42%, the CRi rate was 4% and the MLFS rate was 6%, for a cCR rate of 52%. The median OS was estimated at 19.1 months (95% confidence interval (CI): 10.0 - 26.5 months). These results indicate that pracinostat plus AZA may be an effective regimen in patients with AML unfit for induction therapy. Azacitidine is approved in the EU [Vidaza®, SmPC 2017] and in other countries for the subset of patients with AML with 20-30% of blasts

	[Fenaux, 2009] and in patients ≥ 65 years of age with AML and > 30% blasts who are not eligible for hematopoietic stem cell transplantation [Dombret, 2015]. Based on data generated from these and other AZA studies in older patients with newly diagnosed AML [reviewed in Cruijsen, 2014], AZA is to be considered an acceptable agent for the background therapy in this Phase 3 study. Based on the favorable Phase II data in older patients with AML (Study MEI-004), pracinostat in combination with azacitidine was selected as the experimental treatment group in this Phase III study PRAN-16-52. In order to optimize the interpretation of the final results and to avoid bias in both safety and efficacy reporting, the control group treatment consists of placebo in combination with azacitidine.
Objectives	**Primary Objective:** To show superiority in terms of overall survival (OS) of treatment with pracinostat (Group A – experimental group) versus placebo (Group B – control group) in patients treated with AZA as background therapy. **Secondary Objectives:** • To describe the efficacy of pracinostat evaluating additional efficacy variables • To assess the safety and tolerability • To evaluate the pharmacokinetics of pracinostat and its main metabolites • To assess the possible drug interaction of Pracinostat on the PK of Azacitidine • To perform a health-economic evaluation of treatment and control group
Study Treatments	• **Group A** (experimental): pracinostat + background therapy **Pracinostat**: one 60 mg capsule orally, once a day, 3 times a week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest during each 28-day cycle. • **Group B** (control): placebo + background therapy **Placebo**: 1 capsule orally, once a day, 3 times a week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest during each 28-day cycle. As **background therapy** azacitidine (AZA) will be administered to both treatment groups at a dose of 75 mg/m^2 by SC or IV injection daily for 7 days of each 28-day cycle. Pracinostat/placebo oral administration is to be taken before injection of azacitidine. Dose reduction of pracinostat/placebo, AZA, or both, are allowed in patients who develop drug-related toxicities.

Study Population	**Inclusion Criteria:** Patients must meet the following criteria for study entry: 1. Male or female patient ≥ 18 years of age with newly diagnosed, histologically or cytologically confirmed, AML including *de novo*, secondary to antecedent hematologic disorders, or treatment-related disease with intermediate or unfavorable risk cytogenetics (Appendix B) 2. Unable to receive intensive chemotherapy regimens at enrollment, based on one of the following: I. Age ≥ 75 years, or II. Age < 75 years with at least 1 of the following co-morbidities: a. An ECOG performance status of 2 b. Clinically significant cardiovascular disease defined as: i. Left ventricular ejection fraction (LVEF) ≤ 50%, measured within 3 months prior to Day 1 confirmed by ECHO/MUGA ii. Congestive heart failure requiring medical therapy iii. Chronic stable angina requiring medical therapy iv. Prior cerebrovascular accident with sequelae c. Clinically significant pulmonary disease defined as: i. Forced expiratory volume in 1 second (FEV1) ≤ 65% of expected ii. Lung diffusing capacity for carbon monoxide (DLCO) ≤ 65% of expected Confirmed by pulmonary tests within 3 months prior to Day 1. d. Diabetes mellitus with symptomatic end-organ damage (e.g., retinopathy, nephropathy, neuropathy, vasculopathy) e. Autoimmune inflammatory conditions (e.g., rheumatoid arthritis, systemic lupus erythematous, inflammatory bowel disease, or similar) requiring chronic disease modifying therapy (e.g., etanercept, adalimumab, infliximab, rituximab, methotrexate, or similar) f. Class III obesity defined as a Body Mass Index (BMI) > 40 kg/m^2 g. Renal impairment defined as serum creatinine > 1.3 mg/dL (> 115 µmol/L) or creatinine clearance <70 ml/min, but still fulfilling criterion #7 3. ≥ 20% blasts in bone marrow 4. Peripheral white blood cell (WBC) count < 30,000/µL For cyto-reduction, hydroxyurea is allowed during screening and up to Cycle 1, Days 1-14, to reduce WBC count to < 30,000 µL

	prior to Day 1. After Cycle 1, Day 14, hydroxyurea is prohibited. 5. ECOG performance status ≤ 2 6. Adequate organ function as evidenced by the following laboratory findings: a. Total bilirubin ≤ 2 × upper limit of normal (ULN) or < 3 x ULN for patients with Gilbert-Meulengracht Syndrome b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN 7. Serum creatinine ≤ 1.5 × ULN according to institutional standards or creatinine clearance ≥ 50 mL/min 8. QT-interval corrected according to Fridericia's formula (QTcF) ≤ 450 ms on electrocardiogram (ECG) at Screening 9. Male patient who is surgically sterile, or male patient who is willing to agree with the true abstinence (refrain from heterosexual intercourse) or who uses barrier contraceptive measures during the entire study treatment period and for 3 months after the last administration of study drug, and agree to refrain from donating sperm during the entire study treatment period and for 3 months after the last administration of study drug (Appendix J) 10. Female patient who is of childbearing potential willing to use a highly effective contraceptive measure while participating on study, OR willing to agree with the true abstinence from heterosexual intercourse during the entire study treatment period and for 3 months after the last administration of study drug (Appendix J) 11. Female patient who is of childbearing potential must have a negative serum pregnancy test result within 1 week prior to starting study drug. 12. Willing to provide voluntary written informed consent before performance of any study related procedure not part of normal medical care 13. Willing and able to understand the nature of this study and to comply with the study and follow-up procedures. **Exclusion Criteria:** Patients who meet any of the following criteria will be excluded from study entry: 1. Able to receive intensive induction chemotherapy 2. AML-associated inv(16)/t(16;16)/del(16q), t(15;17) (i.e., promyelocytic leukemia) with/without secondary aberrations; t(8;21) lacking del (9q) or lacking complex karyotypes 3. Presence of an active malignant disease within the last 12 months, with the exception of adequately treated cervical cancer in-situ, non-melanoma skin cancer and superficial bladder tumors (Ta [non-invasive tumor], Tis

	[carcinoma in situ] and T1 [tumor invades lamina propria]). Other malignancies may be considered after consultation with the Medical Monitor 4. Life-threatening illnesses other than AML, uncontrolled medical conditions or organ system dysfunction that, in the Investigator's opinion, could compromise the patient's safety or put the study outcomes at risk 5. Uncontrolled arrhythmias; any Class 3-4 cardiac diseases as defined by the New York Heart Association (NYHA) functional classification (Appendix E) 6. Evidence of AML central nervous system (CNS) involvement 7. Previous therapy for AML except for the following, which are allowed: a. Hydroxyurea for cytoreduction b. One course of hypomethylating agent therapy (i.e.; up to 7 doses of azacitidine or 3-5 days of decitabine) within 30 days prior to enrollment (Day 1) 8. Use of experimental drugs ≤ 30 days prior to screening 9. Received any prior HDAC inhibitor therapy 10. Received prior treatment with a hypomethylating agent, except as allowed in Exclusion Criterion 7.b 11. Known hypersensitivity to any components of pracinostat, azacitidine, or mannitol 12. Human immunodeficiency virus (HIV) infection or an active and uncontrolled infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) 13. Gastrointestinal (GI) tract disease that causes an inability to take oral medication, malabsorption syndrome, or a requirement for IV alimentation; prior surgical procedures affecting absorption; or uncontrolled inflammatory GI disease (e.g., Crohn's disease, ulcerative colitis) 14. Any disease(s), psychiatric condition, metabolic dysfunction, or findings from a physical examination or clinical laboratory test result that would cause reasonable suspicion of a disease or condition, that contraindicates the use of pracinostat and/or AZA, that may increase the risk associated with study participation, that may affect the interpretation of the results, or that would make the patient inappropriate for this study 15. Breast-feeding woman 16. Current smokers (use of patches, chewing gums or vaping nicotine containing fluids is permitted). Patients who stopped smoking at least 8 days prior to first pracinostat dosing can be enrolled, provided they refrain from smoking during the whole study. 17. Prohibited concomitant medications 18. Uncontrolled infections

	19. Received more than 1 prior cycle of HMA or bone marrow transplant for any prior hematological disorder antecedent to AML.
Length of Study	The study duration is dependent on reaching 390 events (deaths) for final survival analysis. It is assumed that recruitment will occur over a 30-months period with 18 additional months to reach 390 events. Patients still on treatment or in follow up at the time of 390 events will enter the Post-Study Observation Period of 24 months.
Assessments and Endpoints	**Efficacy assessments:** • Bone Marrow Aspirate/biopsy Bone marrow aspirate/biopsy sample will be collected for: o morphologic diagnosis of AML and evaluation of morphologic response to therapy o Classical cytogenetic analysis (karyotyping) to assess cytogenetic risk category and allow stratification by cytogenetic risk factor (intermediate vs. unfavorable) at randomization and to evaluate cytogenetic response to therapy in patients with abnormal cytogenetics at baseline o MRD evaluation by MFC o Biobanking for mutational analysis Bone marrow aspirate/biopsy samples are to be collected at screening and then at the end of every even cycle, in order to evaluate the disease response to therapy at the beginning of each odd cycle. Response evaluation assessment is required until a morphologic complete response is achieved and confirmed after 2 further cycles of treatment. At subsequent cycles, bone marrow response evaluation is no longer required, unless there is a suspicion of disease progression or relapse. MRD evaluation will be performed on bone marrow blood only at screening and after 2 cycles from first CR. A small quantity of bone marrow blood will be collected and stored in all patients for potential analysis of mutations of six genes known to have a prognostic impact in patients affected by AML: NPM1, FLT3, CEBPA, RUNX1, ASXL1, TP53. • RBC and platelet transfusions Information regarding red blood cell and platelet transfusions is to be collected on a regular basis. • Quality of Life using the EORTC QLQ-C30 questionnaire The questionnaire is to be administered to the patients during the first visit of each odd cycle. **Safety assessments:** The following safety assessments will be obtained: physical examination,

	vital signs, 12-lead electrocardiogram (ECG), laboratory test (hematology and blood chemistry), and adverse events (AEs) assessments. During the conduct of the study, an Independent Data Monitoring Committee will periodically review safety data. **Pracinostat Population PK assessments:** PK samples are collected in all patients (except for patients participating in AZA/Pracinostat PK sub-study) to characterize the pracinostat population PK and assess the effect of drug exposure on safety and efficacy. The following PK samples are to be collected post pracinostat/placebo administration: • 30 minutes ± 15 minutes • 3 hours ± 30 minutes • 6 hours ± 30 minutes • 24 hours ± 1 hour (before azacitidine) • 48 hours ± 2 hours (before next pracinostat dose) • Day 15 (any time within 24 h after pracinostat dosing for the day) **AZA/Pracinostat PK sub-study (IN SELECTED SITES ONLY): Assessment of the possible drug interaction of pracinostat on the PK of azacitidine.** The azacitidine PK in individual patients with/without the concomitant administration of pracinostat will be studied in two groups of at least 12 patients each. Blood samples will be collected at the following time points on Cycle 1 Day 1 after start of AZA administration: • 15 minutes ± 2 minutes • 30 minutes ± 2 minutes • 1 hour ± 5 minutes • 2 hours ± 5 minutes • 3 hours ± 5 minutes • 4 hours ± 5 minutes • 6 hours ± 30 minutes • 8 hours ± 30 minutes (optional sampling) On Cycle 1 Day 2 before start of AZA administration: • 24 hours ± 1 hour Two additional blood samples will be collected at the following time points on Cycle 1 Day 3 and Day 15: • 48 hours ± 2 hours (before next pracinostat dose intake)

	• Day 15 (any time within 24 h after pracinostat dosing for the day) **Efficacy Endpoints:** • Primary Endpoint The primary efficacy endpoint is the overall survival (OS), as measured from the time of randomization until death from any cause. • Secondary Endpoints Morphologic Complete Remission (CR) rate Transfusion independence Complete Remission without minimal residual disease (CR_{MRD-}) rate Cytogenetic Complete Remission (CRc) rate • Exploratory Endpoints Composite Complete Remission (cCR) rate Relapse Free Survival (RFS) Progression free survival Duration of Morphologic Complete Remission Duration of Composite Complete Remission Time to CR CR within 6 cycles Quality of Life **PK Endpoints:** • To characterize the pharmacokinetics (PK) of pracinostat and its main metabolites in AML patients by a population pharmacokinetic approach • To characterize demographic, physiopathological and therapeutic covariates that may influence pracinostat PK parameters and their interindividual variability • To characterize the pracinostat exposure-response relationship for safety and efficacy endpoints (PK/PD) • To assess the possible drug interaction of pracinostat on the PK of AZA in AML patients by comparing the descriptive statistics of PK parameters of azacitidine in the two groups
Statistical Analyses	**Sample Size:** This is an event-driven study. Sample size was computed for a group-sequential design with stopping rules for both futility and superiority (study-wise one-sided alpha level=0.025, power 0.90) with one interim analysis at 67% (2/3) of information and a final analysis. The error spending function is from the Gamma Family using γ=-3.6 (similar to O'Brien Fleming) for superiority and γ=-5.5 (more conservative than O'Brien Fleming) for futility

	(non-binding). Proportionality of hazards is assumed. Assuming that median OS is 10.0 months in the Group B (placebo + AZA) the aim is to detect, by means of the log-rank test or equivalent, an increase to 14.0 months in Group A (pracinostat + AZA), i.e., a HR of 0.714. A total of 390 events (deaths) allows to meet a power requirement of at least 90% (actually 90.78%) at a study-wise one-sided significance level of 0.025. **Interim Analysis:** An interim analysis at 67% (2/3) of information (260 over 390 events (deaths), being the study event-driven) will be performed for both futility and superiority. **Statistical Evaluation:** Summary statistics for continuous variables will include the mean, standard deviation, median and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages, and time-to-event variables will be summarized using Kaplan-Meier estimates including median with 95% CI, number of events, number censored. Data listings will be created to support each table and to present all data. The primary efficacy endpoint of overall survival will be analyzed using the intent-to-treat (ITT) set. Inferential statistical analysis for treatment group differences will be based on the stratified log-rank test at the alpha = 0.025 level of significance (one-sided) including the stratification factors used for randomization. The unadjusted analysis will be performed as sensitivity analysis. Secondary endpoints will be tested according to a fixed sequence method. If the primary endpoint is statistically significant, then the first secondary endpoint will be tested, and so on for the other three secondary endpoints. A group-sequential procedure will be applied also to the secondary endpoints. Safety analyses will be performed on the Safety Set. Safety variables including treatment-emergent adverse events, laboratory tests, vital signs, and ECGs, will be summarized using appropriate descriptive statistics by treatment group. The statistical analysis plan will provide full details of all planned analyses.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
ALP	ALkaline Phosphatase
ALT	ALanine aminoTransferase
AML	Acute Myeloid Leukemia
ANC	Absolut Neuthrophils Count
Anti-HBc	Antibody against hepatitis B core antigen
Anti-HBs	Antibody against hepatitis B surface antigen
AST	ASpartate aminoTransferase
AUC	Area Under the Curve
AZA	AZAcitidine
BM	Bone Marrow
BMI	Body Mass Index
BSA	Body Surface Area
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CCI	Charlson Comorbidity Index
cCR	Composite Complete Remission
CI	Confidence Interval
CL	Plasma CLearance
CNS	Central Nervous System
CO_2	Carbon diOxide
CR	(Morphologic) Complete Remission
CRc	Cytogenetic Complete Remission
CRi	Morphologic Complete Remission with incomplete blood count recovery
CR_{MRD-}	Complete Remission without minimal residual disease

Abbreviation	Definition
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Lung Diffusion Capacity for carbon monoxide
DMC	Data Monitoring Committee
DNA	DeoxyriboNucleic Acid
DR	Duration of Response
EC	Ethics Committee
ECG	ElectroCardioGram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
e.g.	For example
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
FAB	French-American-British classification
FEV1	Forced Expiratory Volume in 1 second
FDA	Food and Drug Administration
FISH	Fluorescence based In Situ Hybridization
GCP	Good Clinical Practice
GI	GastroIntestinal
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface Antigen
HCT-CI	Hematopoietic Cell Transplant Comorbidity Index
HCV	Hepatitis C Virus
HDAC	Histone DeACetylases
HDACi	Histone DeACetylases inhibitors
HIV	Human Immunodeficiency Virus

Abbreviation	Definition
HMA	HypoMethylating Agent
HR	Hazard Ratio
HSCT	Hematopoietic Stem Cell Transplant
IB	Investigator Brochure
IC_{50}	half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
ITT	Intent To Treat
IND	Investigational New Drug (application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	IntraVenous
IWG	International Working Group
IWRS	Interactive (voice and) Web Response System
K_2EDTA	Di-potassium ethylenediaminetetraacetic acid
LC	Liquid Chromatography
LDAC	Low Dose Cytarabine
LDH	LactatDeHydrogenase
LVEF	Left Ventricular Ejection Fraction
MDS	MyeloDysplastic Syndrome
MedDRA	Medical Dictionary for Drug Regulatory Activities
MedPT	(MedDra) Preferred Term
MFC	Multi-flow cytometry
MLFS	Morphologic Leukemia Free State
MRD	Minimal Residual Disease
MS	Mass Spectrometry
MTD	Maximum Tolerated Dose

Abbreviation	Definition
Na-Heparin	Heparin Sodium
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall Survival
PD	Progressive Disease
PE	Physical Examination
PH	Proportional Hazards
PK	PharmacoKinetic
PK/PD	PharmacoKinetic/Pharmacodynamic
PP	Per Protocol
PLT	Platelet
PR	Partial Remission
Pri	Partial Remission w incomplete blood count recovery
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RAEB	Refractory Anemia with Excess Blasts
RAEB-T	Refractory Anemia with Excess Blasts in Transformation
RBC	Red Blood Cell
RFS	Relapse Free Survival
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	SubCutaneous
SD	Stable Disease
SOC	(MedDra) System Organ Class
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

Abbreviation	Definition
SWOG	SouthWest Oncology Group
TEAE	Treatment-Emergent Adverse Event
THU	Tetrahydrouridine
ULN	Upper Limit of Normal
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
US	United States of America
vs.	Versus
WBC	White Blood Cell
WHO	World Health Organisation

1 INTRODUCTION

1.1 Overview of Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a heterogeneous group of malignancies of the bone marrow. The underlying AML pathophysiology involves a maturational arrest of bone marrow cells in the earliest stages of development of the myeloid-cell lineage. The mechanism of this arrest is poorly understood and involves in many cases the activation of abnormal genes through chromosomal translocations and other genetic abnormalities.

Approximately about 21,380 new cases and 10,590 deaths from AML are expected to occur in the United States (US) in 2017, with the disease most commonly diagnosed in older people [American Cancer Society, 2017]. According to the Surveillance of Rare Cancers in Europe (RARECARE) project, the incidence of AML in Europe is 3.7 per 100,000 [Visser, 2012], similar to an incidence in the US of 4.1 per 100,000 based on 2009-2013 cases [SEER 2016] The average age of patients with AML is 67 years [American Cancer Society, 2017]. AML is a rapidly progressing disease, often fatal, and survival among elderly patients is typically short. Population-based studies have reported 3-year survival rates of 9% to 10% in patients ≥60 years of age, compared with 5-year survival rates of up to 50% for patients <60 years [Luger, 2010]. This poor survival expectancy applies to approximately half of adult patients with AML, in that the median age at onset is 65 to 70 years [Estey, 2014].

Curative therapy for AML, excluding acute promyelocytic leukemia, consists of intensive anthracycline-based remission induction therapy, followed by post remission treatment intensification, including myeloablative therapy and hematopoietic stem cell transplant (HSCT). As AML is a disease of older people, many patients diagnosed with AML are unable to undergo intensive (curative) therapies due to co-morbid conditions and/or poor performance status [Estey, 2002]. In addition, a small proportion of younger patients with AML are unable to receive intensive chemotherapy regimens because of their medical history or concurrent comorbidities that expose them to an increased risk of fatal complications following induction chemotherapy.

In the US, there are currently no drugs approved to treat AML in patients who are unfit for intensive induction chemotherapy. Therefore, participation in clinical studies investigating less toxic and potentially effective therapeutic agents is important for these patients. In the EU, hypomethylating agents (HMAs) (*Dacogen®* - *decitabine, Vidaza®* - azacitidine) are approved for the treatment of adult patients who are not candidates for intensive induction chemotherapy or for hematopoietic stem cell transplant. The efficacy of HMAs alone in this patient population, however, is modest and further improvement is needed. Other approaches for treatment of medically unfit patients with AML include low dose cytarabine (LDAC), clofarabine, and supportive care. As a result, new treatment approaches are needed for this patient population.

1.2 Histone deacetylase inhibitors and Hypomethylating agents

The importance of epigenetic processes, especially those resulting in the silencing of key regulatory genes, has led to the realization that genetics and epigenetics cooperate at all stages of cancer development [Jones & Baylin, 2007].

Histone deacetylases (HDACs) are enzymes involved in the remodeling of chromatin and therefore have a key role in the epigenetic regulation of gene expression. Abnormal epigenetic silencing of important regulatory genes has been described in cancer, including myelodysplastic syndrome (MDS) and AML. Histone deacetylase inhibitors (HDACi) have been extensively studied in both hematologic malignancies and solid tumors. In the US, four HDACi have been approved, all for the treatment of lymphoid malignancies such as cutaneous T-cell lymphoma (vorinostat and romidepsin), peripheral T cell lymphoma (belinostat), or multiple myeloma (panobinostat). No HDACi has been approved in the treatment of myeloid malignancies.

Studies have shown that AML cells demonstrate widespread hypermethylation of DNA promoter regions and that such hypermethylation leads to selective gene silencing. These observations led to the development of HMAs, such as azacitidine and decitabine, which were designed to reverse the hypermethylation and normalize gene expression, particularly in hematologic malignancies. Both of these agents have demonstrated clinical benefit in MDS, but have failed to provide sufficient clinical benefit in AML.

The therapeutic potential of combining HDACi's and HMAs has been studied extensively in pre-clinical models, and synergistic interactions have been described [Cameron, 1999].

1.3 Background on Pracinostat

Pracinostat is a rationally designed, potent, oral, pan-HDAC (including Class I, II, and IV isoforms) inhibitor with favorable pharmacokinetic (PK) properties. In preclinical studies, the activity of pracinostat has been shown in xenograft tumor models of AML and synergistic interactions have been observed with multiple cytotoxic and targeted anti-cancer therapeutics, including azacitidine (Investigator's Brochure). More specifically, the IC_{50} of pracinostat across a broad range of human cancers in *in-vitro* cytotoxicity assays ranged from 0.05 to 2.2 μM, with the lowest values noted in leukemia and lymphoma cell lines. Notably, the combination index with azacitidine (AZA) ranged from 0.44 to 0.55.

Pracinostat has been administered to more than 400 patients, with both solid tumors and hematologic cancers, in multiple Phase I and Phase II clinical studies. The initial safety data for pracinostat monotherapy, which established the single-agent maximum tolerated dose (MTD) and recommended Phase II dose level of 60 mg was derived from Study SB939-2006-001.

SB939-2006-001 was a Phase 1 open-label dose-escalation cohort study of pracinostat in subjects with advanced solid tumors (Arm A) and advanced hematologic malignancies including MDS, AML, lymphoma and myeloproliferative disorders (Arm B). The objectives of the trial included determining the DLTs and MTD of this drug when administered as a single agent, orally, once daily, every other day 3 times a week, for 3

consecutive weeks followed by 1 week rest, for a 28-day treatment cycle. The MTD of pracinostat in Arm A (solid tumors) was established, and the recommended dose is 60 mg/d. In Arm B (hematologic malignancies), the protocol defined MTD was not reached. Dose reductions in subjects at the 120 mg/d level prompted the decision to end the dose escalation phase, designate the 120 mg/d level as the MTD, and identify the recommended dose to be 100 mg/d. However, long-term exposure at 100 mg/d was not well tolerated and the recommended dose in subsequent hematologic malignancy studies was determined to be 60 mg/d.

SB939-2006-001 Arm C investigated the safety and tolerability at the recommended dose of pracinostat (SB939) (60 mg/d) combined with standard azacitidine therapy in subjects with intermediate- or high-risk MDS. Pracinostat was administered orally once daily every other day 3 times a week for 3 consecutive weeks followed by a 1 week rest, for a 28 day treatment cycle. Azacitidine 75 mg/m^2 was administered SC on days 1–5 every 3–6 weeks. Ten subjects (7 female, 3 male) were enrolled with a median age of 65 years (range, 18 to 73 years). There were no DLTs in this study [Quintás-Cardama , 2012].

The most common adverse events (all grades) from the Phase I and Phase II clinical studies of single-agent pracinostat included thrombocytopenia (44%), fatigue (42%), nausea (32%), anemia (30%), and neutropenia (29%). While the most common clinically important (Grade ≥3) adverse events (AEs) included thrombocytopenia (13%), fatigue (9%), neutropenia (9%), and QT prolongation (5%) (Investigator's Brochure). These data collectively support a single-agent dose and schedule of 60 mg, orally, given 3 times a week, every other day for 3 consecutive weeks followed by 1 week of rest and repeated in 28-day cycles. Two of 15 patients with AML treated in Arm B achieved a CR lasting 206 and 362 days.

These patients were enrolled at the 80 mg/day and 120 mg/day dose levels, respectively. One responder required 2 dose reductions due to Grade 3 fatigue, but went on to complete 11 cycles before his death from chronic obstructive pulmonary disease unrelated to pracinostat. The second responder sustained a cytogenetic complete remission (CRc) from Cycle 4 onward and was judged as no longer requiring treatment after completing Cycle 8. These data suggest that single-agent pracinostat provides modest clinical activity in AML.

On the basis of these SB939-2006-001 data, an open-label Phase II study (Protocol MEI 004) has been conducted to evaluate the safety and efficacy of pracinostat plus AZA in patients ≥ 65 years with newly diagnosed AML who were not eligible to receive intensive induction chemotherapy [Garcia-Manero, 2019]. Pracinostat and AZA administration regimen was the same selected in the SB939-2006-001. Pracinostat was administered at a dose of 60 mg every other day, 3 days a week for 3 weeks of every 28-day cycle. AZA was administered according to the approved prescribing information. Between December 2013 and November 2014, a total of 50 patients were enrolled at 15 academic centers in the US. Median age was 75 years (range, 66-84), with 26 patients (52%) aged ≥ 75 years. CR was achieved in 21 patients (42%), a CRi in 2 (4%) and MLFS in 3 (6%), resulting in a composite complete remission (cCR) rate, the study primary endpoint, of 52%. As of October 2016 the median overall survival was estimated at 19.1 months (95% CI: 10.0 - 26.5 months). Grade ≥ 3 adverse events (AEs) reported in > 10% of patients were

thrombocytopenia (46%), febrile neutropenia (44%), neutropenia (38%), fatigue (34%), and anemia (30%). There have been two deaths on study considered related to both pracinostat and azacitidine (neutropenic sepsis and febrile neutropenia).

See the pracinostat Investigator's Brochure for additional details on nonclinical and clinical studies.

1.4 Background on Azacitidine in AML

Azacitidine was approved by the Food and Drug Administration (FDA) in 2004 and the European Medicines Agency (EMA) in 2008 for the treatment of patients with MDS of all French-American-British classification (FAB) subtypes [Vidaza® SmPC, 2017]. Of note, patients with the FAB classification of RAEB-T are considered to meet criteria for AML under the newer World Health Organization (WHO) classification, when the bone marrow blast count is 20% or more [Vardiman, 2009].

Azacitidine is approved in the EU [Vidaza® SmPC, 2017] for a subset of patients with AML, based on two studies. In a retrospective analysis of a study of 358 patients with higher risk MDS which included 113 patients with bone marrow blasts between 20% and 30% [Fenaux, 2009], azacitidine was compared to best supportive care (BSC), BSC + LDAC, or intensive chemotherapy. This study demonstrated an improvement in overall survival (OS) (HR=0.47, p=0.005) in the subset of 113 patients with baseline blasts between 20% and 30%. Another Phase 3 study was conducted exclusively in patients aged ≥ 65 years with AML (>30% marrow blasts) who were not candidates for HSCT [Dombret, 2015]. This study compared azacitidine to BSC, BSC + LDAC, or intensive chemotherapy. The results showed no difference in response rates (CR+CRi: 28% vs. 23%, p=NS) and a trend toward improved overall survival (10.4 vs. 6.5 months; HR=0.85, p=0.1009 for Azacitidine group vs. the composite group). Based on these results, azacitidine is considered as a standard of care in elderly patients with AML, also in countries where azacitidine has not been approved for this indication [National comprehensive Cancer Network Guidelines Acute Myeloid Leukemia. Version 1. 2016.].

It should be noted that 18% of the patient population in the azacitidine study in elderly AML [Dombret, 2015] were assigned to receive intensive chemotherapy (not delineated by age groups) such that the overall prognosis of this study population (both the control and experimental groups) may be superior to other studies of AML in the elderly population that did not permit intensive chemotherapy as a control treatment option [e.g., Kantarjian, 2012; Thepot , 2014].

1.5 Benefit-Risk Assessment

Population-based studies of patients aged 60 years and older have shown 3-year survival rates between 9% and 10% and 5-year survival rates from 3% to 8% [Luger, 2010]. Despite treatment advances in the last decade, the prognosis for older patients remains dismal, and there are only a few approved agents for patients who are unable to tolerate intensive chemotherapy. Thus, there is a great need to explore combinations of novel agents to improve outcomes in this population.

2 STUDY OBJECTIVES

2.1 Primary Objective

To show superiority in terms of overall survival (OS) of treatment with pracinostat (Group A – experimental group) versus placebo (Group B – control group) in patients treated with AZA as background therapy.

2.2 Secondary Objectives

- To describe the efficacy of pracinostat by evaluating additional efficacy variables
- To assess the safety and tolerability
- To evaluate the pharmacokinetics of pracinostat and its main metabolites
- To assess the possible drug interaction of Pracinostat on the PK of Azacitidine
- To perform a health-economic evaluation of treatment and control group

3 STUDY PLAN

3.1 Study Design

This is a Phase III, double-blind, placebo-controlled, multicenter, randomized study of pracinostat in combination with azacitidine (AZA) in patients ≥18 years of age with newly diagnosed acute myeloid leukemia (AML) not fit to receive intensive induction chemotherapy.

A maximum of 500 patients are planned to be enrolled over a period of approximately 30 months at approximately 130 study centers. Patients who meet the eligibility criteria and consent to participate will be randomized 1:1 to Group A (experimental group) or Group B (control group). Randomization will be stratified by cytogenetic risk category (intermediate vs. unfavorable risk) and ECOG Performance Status (0-1 vs. 2).

Study treatment, defined as the treatment with pracinostat/placebo (study drug) in addition to the background therapy (AZA), will continue until there is documented disease progression or relapse from CR while receiving study treatment, or non-manageable toxicity. There is no upper limit to the number of treatment cycles administered, and study treatment should be continued as long as patients derive a clinical benefit.

In the Phase II study MEI-004, 6 patients (12%) required more than 6 cycles of pracinostat + AZA to achieve a CR. It is recommended, therefore, that patients who have no evidence of disease progression should receive a minimum of 6 cycles of study treatment to allow adequate exposure to study drug and background therapy before considering a switch to other therapies.

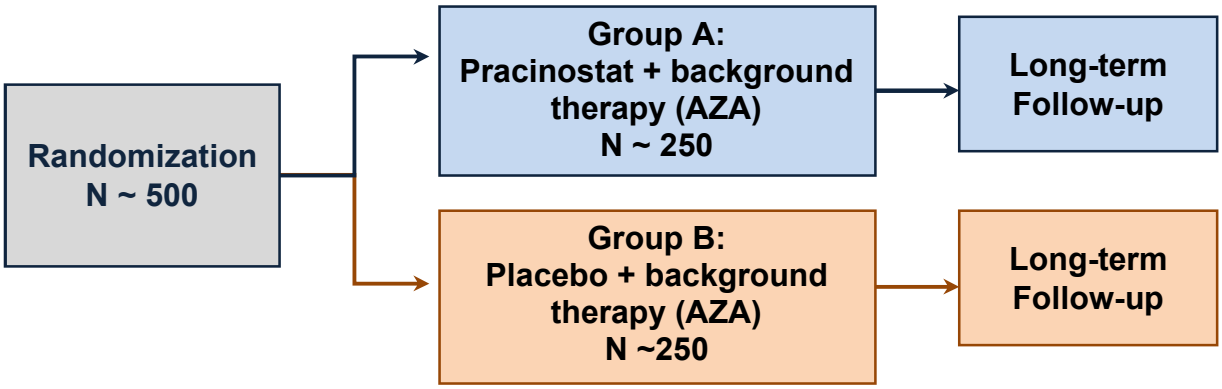
Once permanently discontinued from study treatment, patients will be followed for AEs (for 30 days) and then they will enter the Long-term Follow-up phase of the study (Section 5.2). Patients in the Long-term Follow-up phase of the study will be followed every 3 months (±1 month) for documentation of disease progression, if applicable, and overall survival. Patients will be followed until death or until end of this study (refer to Section 3.2 for end of this study definition).

Based on data from previous studies, it is anticipated that patient participation in the main part of this study will be for an average of 9.5 months, including 28 days for screening procedures, 8 months for study treatment, and 4 weeks for safety follow-up after permanent study treatment discontinuation. In the Phase III study of azacitidine in elderly AML, patients received a median of 6 cycles of azacitidine, with a range from 1 to 28 cycles (Dombret, 2015). In the Phase II study of pracinostat in elderly AML (Study MEI-004), patients received a median of 6.5 cycles, with a range from 1 to 24 cycles. It is anticipated that patient participation in the Long-term Follow-up phase will be for an average of 6 months, but may exceed 12 months in some patients.

This is an event-driven study with an interim analysis for both futility and superiority.

The Schedule of Assessments is provided in Appendix A.
Figure 1 displays the study schema.

Figure 1: Study Schema



3.2 End of Study

The end of this study is defined when 390 events (deaths) have occurred. Patients who are receiving study treatment at the end of the study will continue to receive the study drug to which they were randomized to (Post-Study Observation Period, Section 5.3), until the Sponsor informs the Investigators of the appropriate course of action, based on the study results.

The study may be ended earlier, based on the results of the interim analysis (Section 9.12). In this case the patients still on study will continue unchanged until the Sponsor informs the Investigators of the appropriate course of action, based on the study results.

3.3 Study Rationale

The higher complete remission (CR) rate and longer OS observed in the open-label Phase II study of pracinostat plus AZA in patients ≥ 65 years with newly diagnosed AML compared to historical controls treated with AZA alone, as well as the aggregate safety data from over 150 patients treated with pracinostat plus azacitidine in 4 studies support the evaluation of this combination regimen in a double-blind, placebo controlled, randomized Phase III trial in AML.

3.3.1 Rationale for Patient Population

This Phase III study will enroll patients ≥18 years of age with newly diagnosed *de novo* or secondary AML who are unfit to receive standard induction chemotherapy due to advanced age and/or comorbidities. Secondary AML is defined as secondary to antecedent hematologic disorders such as myelodysplastic or myeloproliferative disorders, or occurring in a patient who has received chemotherapy and/or radiation therapy for a prior malignancy. It is anticipated that the median age of the study population will be approximately 75 years and that few patients under 65 years of age will be enrolled. This population is considered appropriate for this Phase III study, given the limited treatment

options and poor outcome for these patients, whose risk: benefit profile for intensive induction therapy is rarely favorable [Kantarjian, 2010; Pastore, 2014].

3.3.2 Rationale for Definition of Ineligibility for Intensive Induction Chemotherapy

Selection of the most appropriate treatment option for an individual patient with AML is best determined by the treating physician in agreement with the patient based on thorough risk:benefit assessment. However, general principles that define ineligibility for intensive therapy regimens can be delineated in the context of clinical trials.

An expert panel has developed a consensus-based definition of patient unfitness to intensive AML induction chemotherapy [Ferrara, 2013]. Factors considered relevant to defining unfitness to intensive induction chemotherapy include severe cardiac, pulmonary, renal or hepatic comorbidity, cognitive impairment, poor performance status, and any other comorbidity that the physician judges to be incompatible with chemotherapy. Another group has developed a hematopoietic cell transplant specific comorbidity index (HCT-CI) to define patient unfitness to receive myeloablative therapy for AML [Sorror, 2005]. The HCT-CI was evaluated retrospectively in a cohort of older patients with AML [Giles, 2007] and validated in a large cohort of patients with myelodysplastic syndrome [Della Porta , 2011]. Another retrospective analysis of a cohort of 5'480 patients with AML treated between 2000 and 2007 in the US identified age and Charlson comorbidity index (CCI) as significantly associated with early death after leukemia therapy [Oran B, 2012]. This protocol uses a compilation of these previously published criteria to characterize patient unfitness for intensive induction chemotherapy.

Several studies have shown a high rate of early death due to toxicity, ranging from 6% to 18%, in elderly patients with AML treated with standard intensive induction chemotherapy [reviewed in Luger, 2010]. Age ≥ 75 years is associated with particularly high risk of toxicity and has been used as prognostic scoring factor in AML [Kantarjian, 2006; Appelbaum, 2006; Malfuson, 2008]. In this protocol, age ≥ 75 years with or without additional comorbidities is a sufficient criterion to characterize a patient as being unfit for intensive chemotherapy.

For fit patients < 75 years of age, intensive induction chemotherapy is the standard of care. Therefore, only patients who are considered unable to receive intensive induction chemotherapy due to comorbidities that preceded the diagnosis of AML will be eligible to be enrolled in the study. This includes poor performance status, significant impairment of cardiac function (a contraindication to anthracycline-based therapy), significant impairment of pulmonary function (a risk factor for respiratory failure in the presence of infection), or a chronic comorbidity with clinically significant functional impairment or end organ damage.

The study excludes patients with acute promyelocytic leukemia, and AML patients with favorable cytogenetic risks, because they can be effectively managed with alternative standard therapies [Schiller, 2005].

3.3.3 Clinical Rationale

The combination of pracinostat plus AZA was evaluated in a Phase II open-label, single-arm, two-stage, multicenter study in patients aged ≥ 65 years with newly diagnosed AML (Study MEI-004). The favorable efficacy results of this study, with a CR rate of 42%, a composite complete remission (cCR) rate of 52%, and a median overall survival of 19.1 months, indicate that pracinostat plus AZA warrants further evaluation in a Phase III study in AML.

Data from the recent Phase III study of azacitidine versus conventional care regimens in 488 elderly patients with newly diagnosed AML revealed the following Grade 3 to Grade 4 treatment emergent AEs with azacitidine: febrile neutropenia (28%), neutropenia (26.3%), thrombocytopenia (23.7%), pneumonia (19.1%), anemia (15.7%) leukopenia (6.8%), and hypokalemia (5.1%) [Dombret, 2015]. Thus, when comparing safety data from studies of single-agent AZA, single-agent pracinostat, and pracinostat + AZA in combination, the safety profiles appear to be similar. Importantly, no new events of special interest were identified in the combination as compared to single-agent AZA or pracinostat studies, suggesting that the combination is not more toxic than single-agent therapies.

The observations of strong pre-clinical synergy between AZA and pracinostat, and the improved efficacy results from the Phase II study in AML compared to historical controls treated with AZA alone, suggest the combination may provide important clinical benefit in the defined patient population. The combination dose and schedule selected for Phase II development was pracinostat 60 mg orally, given 3 times a week, every other day for 3 consecutive weeks followed by 1 week of rest and repeated in 28-day cycles and azacitidine 75 mg/m^2 IV or subcutaneous (SC) for 7 days of each 28-day cycle. The same regimen will be evaluated in this Phase III study.

Collectively, these safety, tolerability, and clinical activity data support the testing of this combination dose and schedule in a pivotal, fully powered Phase III study in patients who are newly diagnosed with AML and who are not currently candidates for intensive induction chemotherapy.

3.3.4 Rationale for the Control Arm

Based on data from the azacitidine Phase III study in newly diagnosed patients with AML aged ≥ 65 years who are unfit for stem cell transplant therapy [Dombret, 2015] and in patients with AML with 20-30% blasts [Fenaux, 2009], azacitidine [Vidaza® SmPC, 2017] was approved in the EU for a subset of patients with AML. Retrospective studies of azacitidine in patients with AML unfit for intensive chemotherapy [Thepot, 2014; Pleyer , 2015] justify the use of azacitidine as the background therapy and therefore its combination with pracinostat. In order to optimize the interpretation of the final results and to avoid bias in both safety and efficacy reporting, placebo in combination with azacitidine will be used as the control group.

3.4 Eligibility and Enrollment

3.4.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Male or female patients ≥ 18 years of age with newly diagnosed, histologically or cytologically confirmed, AML including *de novo*, secondary to antecedent hematologic disorders, or treatment-related disease with intermediate or unfavorable-risk cytogenetics (Appendix B)
2. Unable to receive intensive chemotherapy regimens at enrollment, based on one of the following:
   I. Age ≥ 75 years, or
   II. Age < 75 years with at least 1 of the following co-morbidities:
      a. An ECOG performance status of 2
      b. Clinically significant cardiovascular disease defined as:
         i. Left ventricular ejection fraction (LVEF) ≤ 50% measured within 3 months prior to Day 1, confirmed by ECHO/MUGA
         ii. Congestive heart failure requiring medical therapy
         iii. Chronic stable angina requiring medical therapy
         iv. Prior cerebrovascular accident with sequelae
      c. Clinically significant pulmonary disease defined as:
         i. Forced expiratory volume in 1 second (FEV1) ≤ 65% of expected
         ii. Lung diffusing capacity for carbon monoxide (DLCO) ≤ 65% of expected

         Confirmed by pulmonary tests within 3 months prior to Day 1.
      d. Diabetes mellitus with symptomatic end-organ damage (e.g., retinopathy, nephropathy, neuropathy, vasculopathy)
      e. Autoimmune inflammatory conditions (e.g., rheumatoid arthritis, systemic lupus erythematous, inflammatory bowel disease, or similar) requiring chronic disease modifying therapy (e.g., etanercept, adalimumab, infliximab, rituximab, methotrexate, or similar)
      f. Class III obesity defined as a Body Mass Index (BMI) > 40 kg/m^2
      g. Renal impairment defined as serum creatinine > 1.3 mg/dL (> 115 µmol/L) or creatinine clearance < 70 mL/min, but still fulfilling criterion #7.
3. ≥ 20% blasts in bone marrow
4. Peripheral white blood cell (WBC) count < 30,000/µL

   For cyto-reduction, hydroxyurea is allowed during screening and up to Cycle 1, Days 1-14, to reduce WBC count to < 30,000 µL prior to Day 1. After Cycle 1, Day 14, hydroxyurea is prohibited.
5. ECOG performance status ≤ 2
6. Adequate organ function as evidenced by the following laboratory findings:

a. Total bilirubin ≤ 2 × upper limit of normal (ULN) or < 3 × ULN for patients with Gilbert-Meulengracht Syndrome
b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN

7. Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min according to institutional standards
8. QT-interval corrected according to Fridericia's formula (QTcF) ≤ 450 ms on electrocardiogram (ECG) at Screening
9. Male patient who is surgically sterile, or male patient who is willing to agree with the true abstinence (refrain from heterosexual intercourse) or who uses barrier contraceptive measures during the entire study treatment period and for 3 months after the last administration of study drug, and agree to refrain from donating sperm during the entire study treatment period and for 3 months after the last administration of study drug (Appendix J)
10. Female patient who is of childbearing potential willing to use a highly effective contraceptive measure while participating on study, or willing to agree with the true abstinence from heterosexual intercourse during the entire study treatment period and for 3 months after the last administration of study drug (Appendix J)
11. Female patient who is of childbearing potential must have a negative serum pregnancy test result within 1 week prior to starting study drug.
12. Willing to provide voluntary written informed consent before performance of any study related procedure not part of normal medical care
13. Willing and able to understand the nature of this study and to comply with the study and follow-up procedures.

3.4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Able to receive intensive induction chemotherapy
2. AML-associated inv(16)/t(16;16)/del(16q), t(15;17) (i.e., promyelocytic leukemia) with/without secondary aberrations; t(8;21) lacking del (9q) or lacking complex karyotypes
3. Presence of an active malignant disease within the last 12 months, with the exception of adequately treated cervical cancer in-situ, non-melanoma skin cancer and superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ] and T1 [tumor invades lamina propria]). Other malignancies may be considered after consultation with the Medical Monitor
4. Life-threatening illnesses other than AML, uncontrolled medical conditions or organ system dysfunction that, in the Investigator's opinion, could compromise the patient's safety or put the study outcomes at risk
5. Uncontrolled arrhythmias; any Class 3-4 cardiac diseases as defined by the New York Heart Association (NYHA) functional classification (Appendix E)
6. Evidence of central nervous system (CNS) involvement
7. Previous therapy for AML except for the following, which are allowed:

a. Hydroxyurea for cytoreduction
b. One course of hypomethylating agent therapy (i.e., up to 7 doses of azacitidine or 3-5 days of decitabine) within 30 days prior to enrollment (Day1)

8. Use of experimental drugs ≤30 days prior to screening
9. Received any prior HDAC inhibitor therapy
10. Received prior treatment with a hypomethylating agent, except as allowed in Exclusion Criterion 7.b
11. Known hypersensitivity to any components of pracinostat, AZA, or mannitol
12. Human immunodeficiency virus (HIV) infection or an active and uncontrolled infection with hepatitis C virus (HCV) or hepatitis B virus (HBV)
13. Gastrointestinal (GI) tract disease that causes an inability to take oral medication, malabsorption syndrome, or a requirement for IV alimentation; prior surgical procedures affecting absorption; or uncontrolled inflammatory GI disease (e.g., Crohn's disease, ulcerative colitis)
14. Any disease(s), psychiatric condition, metabolic dysfunction, or findings from a physical examination or clinical laboratory test result that would cause reasonable suspicion of a disease or condition, that contraindicates the use of pracinostat and/or AZA, that may increase the risk associated with study participation, that may affect the interpretation of the results, or that would make the patient inappropriate for this study
15. Breast-feeding woman
16. Current smokers (Use of patches, chewing gums or vaping nicotine containing fluids is permitted). Patients who stopped smoking at least 8 days prior to first pracinostat dosing can be enrolled, provided they refrain from smoking during the whole study.
17. Prohibited concomitant medications
18. Uncontrolled infections
19. Received more than 1 prior cycle of HMA or bone marrow transplant for any prior hematological disorder antecedent to AML

4 STUDY TREATMENTS

4.1 Study Treatment Groups

Patients will be randomized to one of the following regimens:

- **Group A** (experimental): pracinostat + background therapy

  Pracinostat: one 60 mg capsule orally, once a day, 3 times a week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest of each 28-day cycle. [See Section 4.5 for pracinostat dose reduction]

- **Group B** (control): placebo + background therapy

  Placebo: 1 capsule orally, once a day, 3 times a week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest of each 28-day cycle. [See Section 4.5 for pracinostat dose reduction]

As a **background therapy** azacitidine (AZA) will be administered to both treatment groups at a dose of 75 mg/m^2 by SC or IV injection daily for 7 days of each 28-day cycle. [See Section 4.5 for AZA dose reduction].
Pracinostat/placebo oral administration is to be taken before SC or IV injection of azacitidine.

4.2 Pracinostat and Placebo

4.2.1 Pracinostat and Placebo Supply, Storage and administration

4.2.1.1 Study drug packaging

Study drug will be supplied in form of blistered capsules, packaged in a child-proof wallet card. The wallet card contains overall 9 individually blistered capsules, i.e., the medication to be used for a single treatment cycle of 4 weeks. The packaging solution will allow an easy identification of the 3 capsules to be taken in each of the three treatment weeks (i.e., Week 1-2-3 and Day 1-3-5).

The wallet card has to be considered as a sealed, blinded and appropriately labeled study kit.

Each study kit is patient-specific and carries a single panel label or a booklet label (depending on the area where the kit is supplied) reporting all the necessary information in English as well as in the local languages for clinical site staff and patients. The information reported is fully in accordance with FDA IND regulations, Annex 13 of the Good Manufacturing Practice (GMP) guidelines (published by the Commission in The rules governing medicinal products in the European Community, Volume 4) and any applicable local requirements.

Each study kit reports an identification number; this will allow the management of the drug supply and the drug accountability.

Pracinostat capsules will be supplied by Helsinn Healthcare SA in two strengths of 45 mg and 60 mg. Identically looking placebo capsules will be provided for each pracinostat capsule strength. Placebo formulations are packaged in a fully blinded manner in order to avoid identification of treatment groups.

Study kit label will carry a removable (peel-off) portion to be applied on study drug accountability/administration form in order to certify the correct distribution and administration of the drug. The hospital pharmacist or a designated responsible person from the site staff will be requested to select the IWRS-assigned study kit and provide the drug to the Investigator or designee. The pharmacist or designated responsible person will fill-in the blank space on the study kit label with the patient number generated after randomization confirmation.

Please note that all the details regarding the use of the study kit will be reported in the **Study Drug Manual** to be supplied to each clinical site before the study start.

4.2.1.2 Study drug depot and distribution

Study kit packaging will be performed by PCI Pharma Services (Rockford, IL, US), which will also act as the central depot. In some countries, local depots will be defined and involved in the distribution process of the study kits.

The study kits, together with relevant documentation, will be supplied directly by PCI or by the defined local depot, either to a designated pharmacist at the hospital site or directly to the Investigator or designee, as applicable.

4.2.1.3 Study drug storage

The study kit will be delivered and stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) with excursions permitted to 15º-30º C (59º-86º F), in a secure area with limited access and protected from direct sun light. At the study site, the designated person responsible for storage of the investigational product (the site pharmacist or the Investigator or a designee) should also make sure that study kits are kept separately from the other medications available on site and in no circumstance should be mixed up with any other medications used at the trial site.

4.2.1.4 Study drug allocation through IWRS

Separate randomization lists will be prepared for assignment of treatments to patients and study medication packaging. Sealed cartons (kits) containing the study medications will be prepared according to the packaging list. An appropriate amount of study kits will be supplied to the designated person at the investigational sites at the beginning of the study, with further re-supplies scheduled once the number of available study kits decrease to a pre-set threshold at each site.

Considering each stratum, patients meeting inclusion and not meeting exclusion criteria will be assigned to one of the two treatment groups, in a balanced design (1:1), according to specific procedures using the integrated system of eCRF (electronic CRF) / IWRS (Interactive Web Response System).

On Day 1 of Cycle 1, after confirmation of patient eligibility, the Investigator will get connected to the eCRF/IWRS for randomization and communicate to the system the unique patient identification number (assigned by eCRF/IWRS at the screening visit).

The IWRS will assign the first free randomization number to patient according to the relevant strata and select a study kit number among the kits available at the site and

containing the selected treatment. The unique patient identification number, the study kit number assigned to the patient, the patient randomization number as well as the other patient characteristics, are stored in the system. The randomization procedure is possible only if study kits of both treatments are available at site.

The hospital pharmacist or designated responsible person will select the appropriate study kit based on the number supplied by the IWRS.

Relevant peel-off label from the selected study kit will be attached on the drug accountability log by the pharmacist or designated person to document the correct kit's assignment.

On Day 1 of each subsequent cycle, the Investigator will get connected to the eCRF/IWRS to access the study kit number to be assigned to the patient (i.e., a study kit containing the same treatment as assigned in the first cycle will be automatically selected). For patients requiring a pracinostat dose reduction, this is to be selected during the eCRF/IWRS study drug allocation procedure. The IWRS will then allocate a new study kit from the same treatment group (pracinostat active vs. pracinostat placebo) and communicate the selected study kit number for the new cycle.

Due to the blinded study design, neither the pharmacist, nor the Investigator, the patient or the CRO will know which treatment is administered. The monitor who will check the drug accountability forms will also be blinded with regard to the treatment administered.

4.2.1.5 Study drug intake

Pracinostat/placebo capsules will be self-administered orally, once a day, 3 days a week with approximately 48 hours (+/- 2 hours) between each dose (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest to complete a 28-day cycle.

On Day 1, Day 3, and Day 15 of Cycle 1, and on Day 1 of Cycle 2, pracinostat/placebo capsule must be administered by the study personnel at the study site to allow ECG recording and pharmacokinetic (PK) blood sample collection in relation to pracinostat time of administration (see Sections 6.2.3 and 6.3). On all other days, pracinostat or placebo may be self-administered at home.

Pracinostat/placebo capsule should be taken with water in either a fed or fasted state, at approximately the same time on each of the scheduled dosing days. Capsule should not be chewed or crushed, it should be swallowed whole. If vomiting occurs, no attempt should be made to replace the vomited dose.

Pracinostat or placebo should not be taken with grapefruit or Seville orange. Refer to Section 4.7 for information on precautionary concomitant medications to be taken with pracinostat.

If a dose (pracinostat or placebo) is missed, then that dose should be withheld for that day. Patients should not take the missed dose later on the same day. For example, if a patient does not take a dose on Monday, then the dose should be started on Tuesday, and the subsequent doses should be taken on Thursday and Saturday. Also, if a patient takes a dose on Monday but not on Wednesday, then the next doses should be on Thursday and

Saturday. The doses for the following week can be taken on Monday, Wednesday, and Friday as long as they are taken 48 hours from each other.

Refer to Section 8.2.6.2 for the handling of overdose or incorrect study drug administration.

4.2.1.6 Study drug accountability

Once the study kits are received at the study site, the pharmacist or designated responsible person will sign the drug receipt form and notify via IWRS the clinical supplies receipt. Adequate records of the receipt, dispensation and return of study kits must be maintained throughout the study. Used study kits will be retained until the drug accountability forms have been checked by a designated monitor. Unused study kits remaining at investigational sites at the end of the study will be either destroyed locally, or returned to the depots where they will be destroyed.

At the end of the study, delivery records will have to be reconciled with those of used and returned stocks. Any discrepancy will have to be accounted for. Destruction of unused study kit will be documented in writing, according to FDA IND regulation 21CFR312.59, ICH Good Clinical Practice (GCP) and the drug depot Standard Operating Procedures (SOPs). Any destruction of remaining study medication material is to be first approved in writing by the study Sponsor.

4.2.2 Precautions and Risks Associated with Pracinostat

4.2.2.1 General Signs and Symptoms

The most common related treatment-emergent adverse events (TEAEs) (occurring in ≥10% of subjects) by SOC are gastrointestinal disorders (68%), general disorders and administration site conditions (56%), blood and lymphatic system disorders (46%), investigations (28%) and metabolism and nutrition disorders (24%).

Nausea (48.0%); fatigue (40.0%); thrombocytopenia (38.0%); neutropenia (30.0%); vomiting (26.0%); diarrhea, anemia, febrile neutropenia, and decreased appetite (22.0% each) were the events (by PT) reported in ≥20% of subjects.

Related SAEs occurring in 2 or more subjects were febrile neutropenia (16.0%), fatigue (4.0%), and pneumonia (4.0%).

See the pracinostat Investigator's Brochure for additional details.

4.2.2.2 Hematologic Symptoms

Pracinostat has been associated with myelosuppression including anemia, thrombocytopenia, and neutropenia (including neutropenic fever). Patients should be monitored for adverse hematologic effects, with dose modification allowed as described in Section 4.5.

Since myeloid malignancies may be characterized by thromboembolic events – including disseminated intravascular coagulation and hemorrhage – caution should be taken in concomitant administration of the following:

- Fibrinolysis inhibitors
- Anticoagulant and antiplatelet drugs

4.2.2.3 Gastrointestinal Symptoms

Disturbances of the GI tract, including nausea, vomiting, and diarrhea, have been reported in patients treated with pracinostat. In the Phase II study of pracinostat + AZA in AML, nausea, diarrhea and vomiting were among the most frequently reported manifestations of GI toxicity, with most cases graded as 1 or 2. Standard antiemetic and antidiarrheal medications and appropriate supportive care should be used per normal clinical practice. Pre-existing nausea, vomiting, and diarrhea should be adequately controlled before starting study drug administration.

4.2.2.4 QTc Prolongation/Cardiac Events

The cardiac safety of pracinostat compared to placebo on the QTcF or the individually corrected QT interval (QTcI) was assessed in 43 healthy subjects in study MEI-010. Following single oral doses of 60 and 120 mg pracinostat, there were dose-proportional increases in HR and QTcF, with peak increases that did not correlate with C_{max} (6 and 24 hours postdose for HR and QTcF, respectively). No clinically meaningful effect on PR or QRS intervals or on T-wave morphologies was noted.

Patients with a prolonged QTcF interval > 450 ms at Screening will not be permitted to participate in the study.

Prior to pracinostat administration, hypokalemia, hypophosphatemia and hypomagnesaemia should be corrected and consideration should be given to monitoring potassium and magnesium in symptomatic patients (e.g., patients with nausea, vomiting, diarrhea, fluid imbalance, or cardiac symptoms). Concomitant medications with a known risk of prolonging the QT interval and/or causing Torsades de Pointes are prohibited. In addition, caution should be taken when using concomitant medications with a possible or conditional risk of prolonging the QT interval and/or causing Torsades de Pointes. Medications with a possible or conditional risk may be used at the discretion of the Investigator (Appendix I).

Subjects requiring any medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias.

4.2.2.5 Procreation

Among the observed adverse effects of pracinostat in 28-day repeated oral dose toxicity studies conducted in CD1 mice, also testicular effects were reported (Investigator's Brochure). Investigators should advice male patients to consider cryopreservation of semen.

4.2.2.6 Phototoxicity

Pracinostat was evaluated for phototoxicity in murine fibroblasts, using the neutral red uptake assay, up to a concentration of 100 µg/mL. The calculated IC_{50} value after

exposure with and without irradiation was 22 and 12 µg/mL, respectively. This resulted in a Photo Irritation Factor (PIF) of 0.54 and a Mean Photo effect of -0.004 leading to the classification 'nonphototoxic' (PRAN-17-39). No measures are therefore to be taken to minimize exposure to UV light.

4.3 Azacitidine

4.3.1 Azacitidine Supply, Storage and Administration

According to the local regulation in place in the different countries involved, Azacitidine will be either supplied by the study sponsor, or procured by the clinical site in case the treatment is reimbursed for use in AML by a third party payers (according to the health insurance plan in that country).

4.3.1.1 Azacitidine supply and distribution

Azacitidine to be used for PRAN-16-52 study is provided as commercial packs in form of Lyophilized powder in 100 mg single-use vials for SC or IV administration.

The Azacitidine 100 mg vial has to be considered as patient-specific, i.e., its content (even if partially used) is to be considered for treatment of a single patient only (cannot be shared between two or more patients).

Commercial Azacitidine packs may be purchased by the sponsor from different markets, depending on the local regulation in the country the drug is used. All the commercial packs supplied by Helsinn to the sites will be clearly identified with a label reporting reference to the PRAN-16-52 study and all the necessary information. Each label applied on the pack carries a peel-off portion with reference information to be attached on the drug accountability log by the pharmacist or designated person in order to document the vial's assignment and the global site accountability. This procedure does not apply for Azacitidine directly procured by site, according to local regulation for procurement; in this case the drug accountability log needs anyway to be completed with information regarding the product used for treatment of the patient, i.e., number of vials used, batch number and expiry date.

In case Azacitidine is procured by study sponsor, supply management will be performed by means of IWRS as done for the pracinostat kits. An appropriate amount of vials will be supplied to the designated person at the investigational sites at the beginning of the study, with further automatic re-supplies scheduled once the number of available vials decreases to a pre-set threshold at each site.

Adequate records of the receipt, dispensation and return of the vials must be maintained throughout the study. Used packs will be retained until the drug accountability forms have been checked by a designated monitor. Unused vials remaining at investigational sites at the end of the study will be either destroyed locally or returned to the drug depots where they will be destroyed. At the end of the study, delivery records will have to be reconciled with those of used and returned stocks. Any discrepancy will have to be accounted for.

4.3.1.2 Azacitidine administration

All patients (Group A and Group B) will receive a standard regimen of AZA at 75 mg/m^2 for 7 days of each 28-day cycle. Azacitidine will be administered via SC injection or as an IV infusion. The IV infusions are generally administered over a period of 10-40 minutes.

Azacitidine must be administered on Days 1 through 7 (Schedule 1) of each cycle. If the site is unable to accommodate this schedule, azacitidine may be given as a '5-2-2 schedule' wherein patients receive AZA for 5 consecutive weekdays (Days 1 through 5; Monday-Friday) and resume azacitidine dosing the first 2 weekdays of the next week (Days 8 and 9) of each 28-day cycle (Schedule 2). Switch between Schedule 1 and Schedule 2 during the study period is acceptable.

The daily AZA dose will be calculated based on the patient's weight and height at Day 1 of Cycle 1 (or up to 3 days before). The dose should be recalculated if the patient's weight changes by ≥ 10% during the study. Sites may follow their institutional guidance for assessing the BSA used for dosing.

The Investigator must ensure azacitidine administration information is collected for the study, including dose changes and administration route.

Azacitidine is to be prepared in accordance with the terms of its regional marketing authorization by reconstitution of the lyophilized powder. Detailed information on how to prepare AZA is provided in the Package Insert, Prescribing Information, Summary of Product Characteristics (SmPC) or Country-specific azacitidine label, as appropriate.

Please note, all the details regarding the use of azacitidine will be reported (in local language) in the **Study Drug Manual** supplied to each clinical site before the study start.

4.3.2 Warnings and Precautions for Azacitidine

Prior to the initial AZA administration and at subsequent cycles, complete blood count (CBC), liver chemistries and serum creatinine should be monitored. Detailed information on the risks associated with the use of AZA is provided in the country-specific product labeling.

The following are the relevant Warnings and Precautions listed in azacitidine [Vidaza® SmPC, 2017] product labeling information.

4.3.2.1 Azacitidine Most Frequent Adverse Reactions

Based on the Vidaza® SmPC, 2017, the most frequent non-hematologic adverse reactions reported with AZA included injection site reactions (usually Grade 1-2), gastrointestinal disorders (constipation, nausea, vomiting and diarrhea, usually Grade 1-2), and pyrexia (usually Grade 1-2).

There may be overlapping adverse events between AZA and pracinostat related to myelosuppression, fatigue and gastrointestinal toxicities.

4.3.2.2 Anemia, Neutropenia and Thrombocytopenia

Azacitidine causes anemia, neutropenia, leukopenia and thrombocytopenia (usually Grade 3-4). Complete blood counts for toxicity should be frequently monitored, at a minimum prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage adjustment for subsequent cycles based on nadir counts and hematologic response should be done.

Refer to Section 4.5 for guidance on dose modifications in the presence of toxicity.

4.3.2.3 Toxicity in Patients with Severe Pre-existing Hepatic Impairment

Because azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Safety and effectiveness of azacitidine in patients with MDS and hepatic impairment have not been studied as these patients were excluded from the clinical trials. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

4.3.2.4 Renal Toxicity

Renal toxicity ranging from elevated serum creatinine to renal failure and death has been reported in patients treated with IV AZA in combination with other chemotherapeutic agents for non-MDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium < 3 mEq/L) were observed in 5 patients with chronic myelogenous leukemia treated with AZA and etoposide. If unexplained reductions in serum bicarbonate < 20 mEq/L or elevations of blood urea nitrogen (BUN) or serum creatinine occur, the dosage should be reduced or held.

Patients with renal impairment may be at increased risk for renal toxicity. Also, AZA and its metabolites are primarily excreted by the kidney. Therefore, these patients should be closely monitored for toxicity.

4.4 Duration of Therapy

Because disease response to low intensity chemotherapy regimens such as AZA requires prolonged exposure, patients should receive a minimum of 6 cycles of therapy as long as there is no evidence of disease progression or non-manageable toxicity.

There is no upper limit to the number of study treatment cycles that may be administered. Because there are no data on optimal length of therapy with low intensity chemotherapy, patients who achieve stable disease or an objective response should remain on study treatment as long as they derive a clinical benefit.

Prophylactic therapies and/or study treatment (pracinostat/placebo and azacitidine) dose adjustments (Section 4.5) may be needed to manage treatment-related toxicities and keep patients on therapy as long as they derive clinical benefit.

4.5 Dose Modifications and/or Dose Interruptions

Dose modifications are permitted to manage drug-related toxicities and to improve treatment tolerability in order to maintain the patient on therapy and prolong exposure to study treatment.

Dose modifications in Cycle 1 and Cycle 2 are discouraged to maximize exposure to study treatment and increase the likelihood of achieving an objective response.

Dose reduction is not allowed within each 28-day cycle, but only between cycles.

The Medical Monitor will review with the Investigator any decision to reduce, interrupt, or permanently discontinue either of the two components of the study treatment (pracinostat/placebo or azacitidine).
If a dose modification is required, a dose reduction should be implemented first, as described in the tables below.

One pracinostat dose reduction is allowed as shown in table below:

Table 1: Pracinostat Dose Reduction

Dose Level	Pracinostat/Placebo
Starting Dose	One 60 mg capsule/3 days per week/ 3 weeks in every 28-day cycle
Dose Level -1	One 45 mg capsule/3 days per week/ 3 weeks in every 28-day cycle

Up to two AZA dose reductions are allowed as shown in the table below:

Table 2: AZA Dose Reductions

Dose Level	Azacitidine
Starting Dose	75 mg/m^2 for 7 days of each 28-day cycle
Dose Level -1	37.5 mg/m^2 (50%) for 7 days of each 28-day cycle
Dose Level -2	25 mg/m^2 (33%) for 7 days of each 28-day cycle

Prior to dose reduction, the Investigator must assess if the toxicity is thought to be due to pracinostat, based on the safety information provided in the Investigator Brochure, or AZA, based on the safety information provided in the AZA product labeling. Severe fatigue, anorexia, weight loss, diarrhea, vomiting and QT prolongation are adverse reactions likely related to pracinostat, whereas pyrexia, injection site reaction, constipation and renal toxicity are adverse reactions likely related to AZA. Myelosuppression (i.e., thrombocytopenia, anemia, leukopenia, and neutropenia) has been reported with similar frequency with pracinostat and AZA therapy.

If toxicity is judged by the Investigator as likely related to pracinostat, then the pracinostat/placebo dose should be reduced first (Table 1). If the toxicity is judged by the Investigator as likely related to AZA, then the AZA dose should be reduced first (Table 2). If the Investigator is not able to ascertain the relationship of an adverse reaction to pracinostat or AZA, then dose reduction will begin with AZA, since AZA is administered to all patients whereas pracinostat is administered to only 50% of patients (i.e., those randomized to Group A). If azacitidine dose is reduced first, and it is determined that further dose modifications are still required after two AZA dose reductions, then pracinostat dose should be reduced.

Dose re-escalations are not allowed for either pracinostat or AZA after a dose reduction. If dose reduction is not sufficient to manage toxicity, then dose interruption of both pracinostat and azacitidine is permitted.

If study treatment is delayed due to toxicity, then the first day when treatment is resumed will be defined as Day 1. The subsequent cycles should return to 28 days in length.

4.5.1 Dose Modification or Interruption for Hematologic Toxicity

Dose modification for hematologic toxicity in the setting of AML is not allowed during the first cycle of treatment (Cycle 1) and not recommended in general, unless the patient is in remission as dose delays and/or reductions may decrease exposure to therapeutically effective levels of drugs.

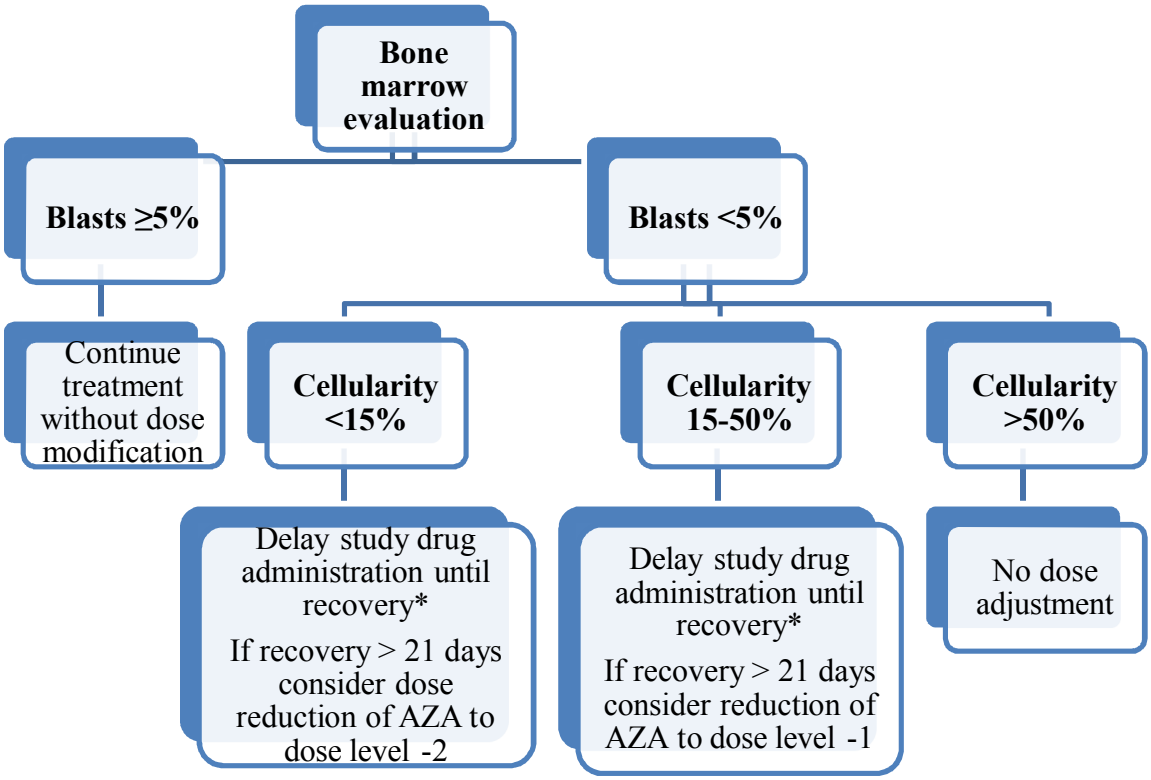
Since myelosuppression (i.e., thrombocytopenia, anemia, leukopenia, and neutropenia) has been reported with similar frequency with pracinostat and AZA therapy, the AZA dose should be reduced first.

From cycle 2 onwards the following criteria are recommended:

a) **Subjects with baseline ANC <1,500 cells/µL or platelets <75,000 cells/µL** and have a ≥ Grade 3 decrease in cell counts before starting next treatment cycle:

   1. ≤50% decrease: may continue treatment with no delay or dose adjustment.
   2. **>50% decrease and a bone marrow evaluation is not required per study protocol**: delay treatment. If recovery is achieved within 14 days, no dose adjustment is required. If recovery is not achieved within 14 days, at day 42 a bone marrow evaluation is suggested and dose adjustment is outlined in Figure 2.
   3. **>50% decrease and a bone marrow evaluation is required per study protocol**: follow dose adjustment outlined in Figure 2.

Figure 2: Dose Adjustment



*Recovery= count ≥ nadir count + [0.5 x (baseline count – nadir count)]

b) **Subjects without reduced baseline counts (ANC ≥ 1,500 cells/µL and platelets ≥ 75,000 cells/µL)** and have a ≥ Grade 3 decrease in cell counts before starting next treatment cycle: delay treatment. If recovery is achieved within 14 days, no dose adjustment is required. If recovery is not achieved within 14 days the dose should be adjusted as follows:

1. **ANC >1.000 cells/µL and PLT >50.000 cells/µL:** no dose adjustment is required;
2. **ANC ≤ 1.000 cells/µL and/or PLT ≤ 50.000 cells/µL:** consider reduction of AZA to dose level -1.

If it is determined that further dose modifications are still required after two AZA dose reductions, then pracinostat dose should be reduced. Unless a patient achieves < 5% blasts in the bone marrow, a cycle should not be interrupted beyond 28 days due to hematologic toxicity.

Patients with drug interruptions for prolonged myelosuppression (defined as > 56 days [2 cycles] with ANC < 500/mm^3 or platelet count < 10.000/mm^3 in a bone marrow with <

5% blasts and no evidence of disease or dysplasia), may only restart treatment after discussion with the Medical Monitor.

4.5.2 Dose Modification or Interruption for Non-Hematologic Toxicity

From Cycle 2 onwards in case of Grade ≥ 3 non-hematologic toxicities a dose reduction or, as subsequent option, a dose interruption of both pracinostat and azacitidine is permitted, after prior discussion with the Medical Monitor.

Patients with Grade ≥3 non-hematologic toxicities may have both pracinostat/placebo and azacitidine held up to a maximum of 4 weeks, or until return to Grade 1 or baseline (whichever comes first). However, in patients who are experiencing a reduction in marrow blasts but have not achieved counts < 5%, dose interruptions beyond 28 days are permitted, but require prior discussion with the Medical Monitor.

- If unexplained reductions in serum bicarbonate levels (or carbon dioxide - CO_2- if bicarbonate is not routinely measured at the site) to <20 mmol/L occur, then the AZA dose should be reduced by 50% for all subsequent cycles.
- If unexplained elevations of urea/BUN or serum creatinine to ≥ 2-fold above baseline values and above ULN occur, then the next cycle should be delayed until values return to normal or baseline and the AZA dose should be reduced by 50% for all subsequent cycles.
- When a QT prolongation is observed for the first time, the patient should be followed with additional ECGs as determined by the Investigator. Both pracinostat/placebo and azacitidine should be held in patients who develop any of the following, unless there is a clear alternative cause for the changes:
    - Sustained (at least two ECG measurements, approximately 30 minutes apart) QTcF that is ≥ 500 ms and/or > 60 ms longer than the baseline value at screening
    - New ECG finding of clinical concern.

Study drug and azacitidine may be resumed when QTcF returns to baseline (i.e., 450 ms in case of absolute increase ≥ 500 ms or the patient's screening value +30 ms in case of increase > 60 ms), any other ECG abnormalities have been resolved, and underlying causes have been addressed, the patient remains clinically stable and is appropriately monitored. Clinical judgment should be applied.

4.5.3 Dose Interruption in Patients with < 5% Bone Marrow Blasts ("Drug Holiday")

A single dose interruption of study treatment for up to 1 cycle (28 days) is allowed but is not recommended in patients who request a "Drug Holiday" and meet all the following criteria:

- Received a minimum of 12 cycles of pracinostat/placebo + azacitidine
- Achieved BM blasts < 5% (i.e., CR, CRi or MLFS)
- Have been in clinical remission (CR, CRi, MLFS) for a minimum of 3 cycles

- If abnormal cytogenetics at baseline, have achieved a cytogenetic CR (CRc)

Both pracinostat/placebo AND AZA must be interrupted during this Drug Holiday. Also, no other treatments for AML, including another investigational product from a different research study, may be administered during this Drug Holiday. Patients who receive another treatment for AML during the Drug Holiday must be discontinued from the active phase of the study and will enter the Long-term Follow-up. Every effort should be made to complete the End of Study Treatment visit **prior** to the patient starting any AML treatment regimen other than pracinostat/placebo + AZA.

Prior to starting the "Drug Holiday", the Drug Holiday Commencement visit (Section 5.1.13.1) must be completed. This study visit should occur on Day 1 of a cycle. For example, if the patient is at Cycle 18 Day 8, then the patient should complete the remaining study visits for that cycle, including study treatment administration (pracinostat/placebo + AZA).

To monitor patients for safety and potential disease progression during the Drug Holiday, study visits must be performed within 4 weeks (+/- 4 days) (Section 5.1.13.2).

When patients complete the Drug Holiday period, they will resume their randomized study treatment assignment, i.e., pracinostat/placebo + AZA. Patient may resume study treatment during the Drug Holiday period at any time after disease evaluation.

4.6 Management of Toxicity

Patient management, including transfusions, use of growth factors, prophylaxis and treatment of infections, will be performed according to institutional guidelines. Palliative and supportive care for disease related symptoms may be administered at the Investigator's discretion and institutional guidelines.

4.6.1 Prophylactic Therapies

Patients should be pre-medicated for nausea and vomiting. Other prophylactic measures (i.e., anti-infectives) may be used as indicated.

4.7 Prior and Concomitant Medications

Information about prior and concomitant medication is to be collected from 28 days prior to Day 1 of Cycle 1 up to the End of treatment visit (Section 5.1.14) and recorded in the CRF.

Infusion of blood products is to be recorded. Particular attention should be paid to the collection of information regarding red blood cell and platelet transfusions: specifically date of transfusion, type of transfusion (red blood cells or platelets), and number of events (e.g., 2 units of red blood transfused at the same moment are considered as one transfusion event).

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All medications administered in relation to diagnostic procedures, e.g., anesthetics and antibiotics are to be recorded.

Prophylactic infusion of saline solution prior to chemotherapy in order to prevent toxic reactions related to chemotherapy should be recorded as well.

4.7.1 Medications Affecting Metabolism of Pracinostat via Cytochrome P450

Few clinical information is available on drug interactions for pracinostat. Pracinostat is substrate of cytochrome P450 1A2 (CYP1A2), P450 2C8 (CYP2C8) and cytochrome P450 3A4 (CYP3A4). Caution in use of pracinostat is required with drugs that inhibit 3A4 and 2C8 or induce CYP1A2, 2C8 and 3A4 (see Investigator Brochure and study PRAN-17-14). Lists of 3A4 and 2C8 inhibitors and 1A2, 2C8 and 3A4 inducers are provided in Appendix G.

Patients should avoid grapefruit juice and Seville oranges during the study since they are known to be inhibitors of CYP3A4.

Smoking results in CYP1A2 induction and has been shown to decrease pracinostat Cmax and AUC by ~60%. This effect is known to be caused by substances created by tobacco smoke, such as polycyclic aromatic hydrocarbons (potent inducers of CYP1A2, a primary CYP450 isoform responsible for pracinostat metabolism). Therefore, current smokers are excluded from the study but the use of patches, chewing gums or vaping nicotine containing fluids is permitted. Patients who stopped smoking at least 8 days prior to first pracinostat dosing can be enrolled, provided they refrain from smoking during the entire study.

4.7.2 Possible Effects of Pracinostat on Other Drugs via Cytochrome P450

In hepatocytes pracinostat is an inducer of CYP1A2 and CY2B6, while is a suppressor of CYP3A4 mRNA expression and enzymatic activity (see Investigator Brochure and PRAN-17-04).

Pracinostat should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when co-administered with pracinostat. Lists of CYP3A4 substrates are provided in Appendix H.

Pracinostat should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP1A2 and CY2B6. The plasma concentrations and the efficacy of CYP1A2 and CY2B6 substrates can decrease when co-administered with pracinostat. Lists of CYP1A2 and CYP2B6 substrates are provided in Appendix H.

4.7.3 Prohibited Concomitant Medications

The following treatments and/or medications are prohibited while on study:

- Any other investigational product taken within 4 weeks prior to Day 1 of Cycle 1 and/or through the entire study treatment period is not allowed. For this purpose “Other investigational product" has to be intended as any agents tested in clinical trials, even those which are tested for indications that are already approved.

- Anticancer agents. If such agents are required, then the patient must discontinue study treatment prior to receiving the anti-cancer therapy and disease progression should be documented. For patients at Cycles 1 through 6, it is recommended to contact the Medical Monitor prior to study treatment discontinuation. Every effort should be made to complete the End of Study Treatment visit **prior** to the patient starting any AML treatment regimen other than pracinostat/placebo + AZA.
- Hydroxyurea is allowed until Cycle 1, Days 1-14, to reduce WBC count to <30,000 µL prior to Day 1. After Cycle 1, Day 14, hydroxyurea is prohibited.

- HDAC inhibitors.
- Medications with a known risk of prolonging the QT interval and/or causing Torsades de Pointes. (Appendix I).
- Herbal products are not allowed throughout the study. Subjects should stop using these prior to the first dose of study treatment.

4.8 Treatment compliance

During each cycle a patient will be considered to be compliant with therapy if s/he takes at least 8 of the 9 capsules of study drug provided in the clinical study medication kit and at least 6 of the 7 AZA doses.

5 STUDY CONDUCT

This study will consist of three phases: Screening, Treatment, and Long-term Follow-up. During the treatment phase, there is a ±4-day window, while during the Long-term Follow-up there is a ± 1-month window for the visits/calls.

5.1 Study Procedures

5.1.1 Informed Consent

Prior to performing any study-specific evaluation, written informed consent is to be obtained from each patient. The consent may be obtained at the earliest one week before the start of screening activities.

5.1.2 Screening Assessments

Screening examinations will only be performed after the patient has given written Informed Consent.

The following evaluations and procedures will be performed within 28 days prior to the first study treatment administration (Cycle 1 Day 1):

- Obtain demographic information: age, gender, and self-reported race/ethnicity
- Collect medical history, concomitant illnesses, prior surgeries, and smoking status: clinically significant diseases, prior cancer history, including cancer therapies and relevant procedures, should be collected
- Assess protocol-qualifying comorbidities. This may require measurement of the left ventricular ejection fraction (LVEF) and/or pulmonary function tests (ECHO/MUGA and/or pulmonary function tests are required to satisfy inclusion criteria IIb and IIc)
- Perform a complete physical examination (Section 6.2.1)
- Obtain vital signs (Section 6.2.2), including height, weight, blood pressure (sitting or in semi-supine position), pulse rate, and body temperature
- Assess ECOG performance status
- Obtain 12-lead ECG in triplicate (Section 6.2.3)
- Collect information about prior and concomitant medications (Section 4.7)
- Assessment of adverse events
- Collect adequate bone marrow aspirate/biopsy (Section 6.1.1)
    - Morphologic diagnosis of AML (a morphologic evaluation of bone marrow already performed within 30 days prior to the ICF signature will be accepted as screening evaluation)
    - Classical cytogenetic analysis - karyotyping (central evaluation) to assess cytogenetic risk category and allow stratification by cytogenetic risk factor (intermediate vs. unfavorable) at randomization and to evaluate cytogenetic response to therapy in patients with abnormal cytogenetics at baseline. If a bone marrow aspirate sample at screening has been already submitted for central cytogenetic analysis but the result is not available to confirm patient eligibility

and a local cytogenetic analysis (karyotyping) has been already performed as per clinical routine within 30 days prior to the ICF signature, the local result will be considered acceptable to enroll the patient. In case of discrepancy between the local and the central result of the baseline cytogenetic analysis leading to different cytogenetic risk categories, the patient should be randomized in the risk category defined by the central assessment. In case the central result should not be available, the local result will be used for randomization.

- Unknown cytogenetic risk results according to SWOG classification will be stratified as intermediate risk, as suggested by ELN 2017 classification.
- MRD panel determination
- If no bone marrow blood can be aspirated at screening ("dry tap", even at repeated attempts) the patient will be considered a screen failure.

- Biobanking for mutational analysis (mandatory in all patients). Peripheral blood and bone marrow fluorescence in situ hybridization (FISH) analysis for cytogenetic study and molecular analysis are not required. However, if FISH testing or molecular analysis are part of the institution's standard of care, the results will be recorded in the Case Report Forms.

The following evaluations and procedures will be performed **within 8 days prior** to the first study treatment administration (Cycle 1 Day 1):

- Laboratory assessments (Section 6.2.4)
- Serum pregnancy test for women of childbearing potential (Section 6.2.4)

Screening evaluations must be completed and patients must meet all eligibility criteria prior to randomization. Eligibility criteria, including the co-morbidities that define unfitness to receive intensive induction chemotherapy, must be reviewed and approved by the Medical Monitor prior to randomization.

Re-screening of a patient who has previously failed study entry will require appropriate discussion with the Medical Monitor and will be approved on a case by case basis.
If one or more screening laboratory tests do not support eligibility, laboratory re-test is permitted only once. Only the laboratory tests which resulted out of range need to be repeated.
In case of re-screening of a patient after one course of hypomethylating agent therapy, all the screening assessments need to be repeated, excluding cytogenetic test.

- Biomarker analysis (if consent obtained by patient): Peripheral blood samples and/or aspirate bone marrow samples will be collected and stored for potential molecular studies (Section 6.4)

5.1.3 Cycle 1 on Day 1

After confirmation of eligibility, the patient will be randomized to one of the two treatment groups using the IWRS. The following activities are to be performed **before study treatment administration**:

- Assess transfusions of red blood cells or platelets performed during the previous 8 weeks (Section 6.1.2).
- Perform a limited physical examination
- Measure blood pressure and pulse rate –**pre-dose** (sitting or in semi-supine position), body temperature, and weight
- 12-lead ECG measurement in triplicate **- pre-dose**
- Collect concomitant medications and any new medical conditions since the screening visit
- Assess ECOG performance status
- Administer the Quality of Life questionnaire
- Urine pregnancy test for women of childbearing potential – **pre-dose**
- Re-check of all eligibility criteria
- Assessment of adverse events
- Randomization via IWRS: The IWRS will provide the investigator with the kit number stored in the site stock to be dispensed to the patient.
- Treatment administration: The study treatment administration schedule is the following:
    - Pracinostat/placebo administration (see Section 4.2): according to the indication reported on the study kit internal panel, the patient will receive 1 capsule of study drug or matching placebo (week 1, day 1). Patient must begin study treatment within 24 hours after randomization.
    - Azacitidine administration: according to indication reported in Section 4.3.1.2 azacitidine is administered to patient.

  Pracinostat/Placebo oral administration is to be taken before administration of azacitidine.

  The date and the precise time (hh:mm) of the study drug and Azacitidine administration as well as other information related to the quantity and origin of the Azacitidine vials must be recorded in the source records as well as on the relevant eCRF page for each medication given. The relevant peel-off labels from the study kit and from the Azacitidine commercial packs used for the treatment at this visit will be attached to the drug accountability log (pharmacist or designated responsible).

Activities to be performed **after study drug administration (for all patients EXCEPT those participating in the AZA/pracinostat PK sub-study.** See Section 6.3**)**:

- Collect three pharmacokinetic (PK) blood samples:
    - 30 minutes (± 15 minutes) **post** pracinostat/placebo administration
    - 3 hours (± 30 minutes) **post** pracinostat/placebo administration
    - 6 hours (± 30 minutes) **post** pracinostat/placebo administration

(IN SELECTED SITES ONLY) AZA/pracinostat PK sub-study: Assessment of the possible drug interaction of Pracinostat on the PK of Azacitidine (See Section 6.3.2):

- Collect 8 pharmacokinetic (PK) blood samples:
  - 15 minutes (± 2 minutes) **post** pracinostat/placebo and AZA administration
  - 30 minutes (± 2 minutes) **post** pracinostat/placebo and AZA administration
  - 1 hour (± 5 minutes) **post** pracinostat/placebo and AZA administration
  - 2 hours (± 5 minutes) **post** pracinostat/placebo and AZA administration
  - 3 hours (± 5 minutes) **post** pracinostat/placebo and AZA administration
  - 4 hours (± 5 minutes) **post** pracinostat/placebo and AZA administration
  - 6 hours (± 30 minutes) **post** pracinostat/placebo and AZA administration
  - 8 hours (± 30 minutes) **post** pracinostat/placebo and AZA administration (optional sampling)
- Triplicate ECGs will be done **90 minutes** (± 30 minutes) and 6 hours (± 30 minutes) **post** pracinostat/placebo administration.
- Measure blood pressure and pulse rate (sitting or in semi-supine position), **90 minutes** (± 30 minutes) **post** pracinostat/placebo administration.

5.1.4 Cycle 1 on Day 2

The following activities are to be performed on Day 2 of the first cycle:

- Collect one PK blood sample at 24 hours (± 1 hour) **after** the first pracinostat/placebo dose, **prior** to AZA administration **(for all patients EXCEPT those participating in the AZA/pracinostat PK sub-study.** See Section 6.3**)**
- Collect one PK blood sample at 24 hours (± 1 hour) after the first pracinostat/placebo dose, **prior** to AZA administration **(IN SELECTED SITES ONLY)** AZA/pracinostat PK sub-study (See Section 6.3.2)
- Triplicate ECGs will be done at **24 hours** (± 1 hour) **after the first** pracinostat/placebo administration, **prior** to AZA administration
- Administer the second AZA dose. Administration should be performed 24 hours (± 1 hour) after the first dose.
- Review concomitant medications since the previous study visit
- Assess AEs since the previous visit

5.1.5 Cycle 1 on Day 3

The following activities are to be performed on Day 3 of the first cycle:

- Collect one PK sample at 48 hours (± 2 hours) after the first pracinostat/placebo dose, **prior** to second pracinostat administration (for all patients, including those in the AZA PK sub-study)
- Pracinostat/placebo administration, 48 hours (± 2 hours) after first pracinostat/placebo dose and after PK sampling

- Triplicate ECGs will be done at **48 hours** (± 1 hour) **after the first** pracinostat/placebo administration, **prior** to AZA administration
- AZA administration (to be administered after PK sample collection)
- Review concomitant medications and therapies (in particular transfusions) since the last study visit
- Assess AEs since the previous visit
- Hand-out to the patient the study medication for the first cycle and give clear instructions regarding the intake (see Section 4.2.1.2).

5.1.6 Cycle 1 on Days 4 to 7 (or 9)

- Pracinostat/placebo administration
- Review concomitant medications since the previous study visit
- Assess AEs since the previous visit
- Administer azacitidine according to the chosen schedule (1-7 or 5-2-2)

The Investigator must ensure azacitidine administration information is collected for the study, including dose changes and administration route.

5.1.7 Cycle 1 on Day 15

The following activities are to be performed on Day 15 of the first cycle:

- Body temperature measurement
- Central laboratory assessment – pre dose
- Pracinostat/placebo dosing
- Blood pressure and pulse rate (in sitting or in semi-supine position) to be measured **90 minutes** (± 30 minutes) **post** pracinostat/placebo administration
- 12-lead ECG measurement in triplicate at **90 minutes** (± 30 minutes) **post** pracinostat/placebo administration
- Collect one PK sample: any time within 24 h after pracinostat/placebo dosing (for all patients, including those in the AZA PK sub-study)
- Assess AEs since the last study visit
- Review concomitant medications since the last study visit
- Assess study drug dosing compliance

5.1.8 Cycle 2 and All Subsequent Cycles on Day 1

At every Cycle, Day 1 visit, the following will be collected and/or performed (unless specified differently):

- A limited physical examination
- Body temperature and body weight measurement

- Blood pressure and pulse rate (in sitting or in semi-supine position) to be measured **predose (Cycle 2 only)**
- 12-lead ECG measurement in triplicate – **predose (Cycle 2 only)**
- Central laboratory assessments – **predose (Cycle 2 only)**
- Serum pregnancy test for women of childbearing potential (Section 6.2.4) **(Cycle 2 only)**
- Assess ECOG performance status
- Assess pracinostat/placebo dosing compliance for the previous cycle
- Review concomitant medications and concomitant therapies (including transfusions) since the last study visit
- Assess AEs since the last study visit
- Administer study drug (pracinostat/placebo) and AZA
- Blood pressure and pulse rate (in sitting or in semi-supine position) to be measured **90 minutes** (± 30 minutes) **post** pracinostat/placebo administration
- 12-lead ECG measurement in triplicate at **90 minutes** (± 30 minutes) **post** pracinostat/placebo administration **(Cycle 2 only)**

After patient has been re-evaluated, including review of laboratory parameters results, the Investigator will get connected to the IWRS for the assignment of a new study kit. The patient will be administered the same treatment assigned at Cycle 1 (active or placebo), but in case the dose reduction from 60mg to 45mg is considered to be necessary by the Investigator, this needs to be reported into IWRS according to dedicated section. The procedures to be completed are the same as for Cycle 1 (Day 1, Visit 2), except for randomization, i.e., for new cycle IWRS will only provide a new kit number for the patient according to the patient's randomization at Cycle 1.

5.1.9 Cycle 2 and All Subsequent Cycles on Days 2 to 7 (or 9)

- Pracinostat/placebo administration
- Review concomitant medications and therapies since the last study visit
- Assess AEs since the previous visit
- Administer azacitidine as detailed in Section 4.3.1.2 according to the chosen schedule (1-7 or 5-2-2)

The Investigator must ensure azacitidine administration information is collected for the study, including dose changes and administration route.

5.1.10 Cycle 2 and All Subsequent Cycles from Day 21 to 26

The last visit during Cycle 2 and following Cycles is to be scheduled within Day 21 and Day 26 (included) ensuring that the results of the performed analyses are available at the time of Day 1 of subsequent Cycles.

From Day 21 to 26 of each cycle, the following will be collected and/or performed (unless specified differently):

- 12-lead ECG measurement in triplicate at any time during the visit **(cycle 2 only)**
- Blood pressure and pulse rate (in sitting or in semi-supine position) to be measured at any time **(cycle 2 only)**
- Central laboratory assessments
- Serum pregnancy test for women of childbearing potential (Section 6.2.4)
- Assess AEs since the last study visit
- Review concomitant medications and concomitant therapies (including transfusions) since the last study visit

5.1.11 Cycle 2 and Subsequent Even Cycles from Day 21 to 26

- Response evaluation

Patients will be evaluated for disease response on Day 1 of each odd Cycle.

To assess response to therapy, a bone marrow aspirate/biopsy has to be performed between Day 21 and Day 26 of each **Even** Cycle (i.e., Cycles 2, 4, 6, 8 …)

If the aspirate is a dry tap, then a bone marrow biopsy is required for the pathology interpretation of response, including bone marrow blasts.

Morphologic response evaluation is required until a complete remission is achieved and confirmed after 2 further cycles of treatment. At subsequent cycles, a bone marrow evaluation is no longer required, unless there is a suspicion of disease progression or relapse.

Classical Cytogenetic (karyotyping), with analysis of preferably 20 metaphases, is to be performed only if the screening cytogenetic test result was abnormal. After the patient has achieved a cytogenetic complete remission, the cytogenetic evaluation is no longer required at subsequent cycles.

MRD evaluation will be performed only 2 cycles after first CR.

A small quantity of bone marrow aspirate will be collected for biobanking for mutational analysis (mandatory in all patients).

FISH as part of cytogenetic testing and molecular analysis are not required. However, if FISH testing or molecular analyses are part of the patient's standard procedure, then the results will be recorded in the Case Report Form.

Since transfusion independence is required to differentiate CR from CRi or MLFS, transfusions of red blood cells or platelets in the preceding weeks must be assessed.

- Biomarker analysis (if consent obtained by patient): Peripheral blood samples and/or aspirate bone marrow samples will be collected and stored for potential molecular studies (Section 6.4).

5.1.12 Cycle 3 and Subsequent Odd Cycles on Day 1

In addition to the data collected at each cycle, the following will be collected and/or performed on Day 1 of every **Odd** Cycle (i.e., Cycles 3, 5, 7, 9 …):

- Single 12-lead ECG measurement at **90 minutes** (± 30 minutes) **post** pracinostat/placebo administration
- Administer the Quality of Life questionnaire

5.1.13 Study Treatment Interruption/ Drug Holiday Schedule

If requested by the patient and with Investigator discretion, a unique Drug Holiday (i.e., period of study treatment interruption) of pracinostat/placebo + AZA for up to 1 cycle (28 days) is allowed, but not recommended, as described in Section 4.5.3.

The start of a Drug Holiday must begin on Day 1 of a scheduled treatment cycle.

When a patient starts a Drug Holiday schedule, the following study visits must be completed: Drug Holiday Commencement Visit (refer to Section 5.1.13.1) and Drug Holiday Follow-up Visits (refer to Section 5.1.13.2).

5.1.13.1 Drug Holiday Commencement Visit

The following procedures must be completed during this visit, which coincides with the Day 1 visit of that cycle:

- Verify patient achieved a clinical remission (i.e., < 5% blasts and no circulating blasts) for a minimum of 3 cycles, and if abnormal cytogenetics at enrollment, achieved a cytogenetic CR
- Verify patient completed at least 12 cycles of pracinostat/placebo + azacitidine
- Perform a complete physical examination
- Obtain vital signs, including weight, blood pressure (sitting or in semi-supine position), pulse rate, and body temperature
- Assess ECOG performance status
- Administer the Quality of Life questionnaire
- Assess AEs since the last study visit
- Review concomitant medications since the last study visit
- Assess study drug dosing compliance at prior cycle
- Collect all unused study drug

Note: any AE occurrences should continue to be collected and reported during the Drug Holiday period.

5.1.13.2 Drug Holiday Follow-up Visits

The Drug Holiday Follow-up Visits will occur within 4 weeks (+/- 4 days) from Drug Holiday Commencement Visit and in any case before resuming the study treatment.

The following procedures must be completed:

- Confirm patient has not taken or started another treatment regimen for AML, including another investigational product.

- Obtain vital signs, including weight, blood pressure (sitting or in semi-supine position), pulse rate, and body temperature
- Assess ECOG performance status.
- Administer the Quality of Life questionnaire
- Central laboratory assessments
- Assess AE occurrence(s) since last contact
- If there is a suspicion of AML recurrence based on CBC results or clinical findings, a bone marrow biopsy/aspirate must be obtained to verify disease progression. In case of disease relapse from CR, patient will proceed with end of treatment visit.

5.1.14 End of Treatment Visit

Study treatment will continue until there is documented disease progression or relapse from CR while receiving study treatment, or non-manageable toxicity.

End of treatment evaluations are required 30 days (+/- 2 days) after treatment ends or prior to starting new treatment, if urgent treatment is required.

The following procedures will be completed:

- Obtain vital signs
- Assess ECOG performance status.
- Administer the Quality of Life questionnaire
- Central laboratory assessments
- For women of childbearing potential, a highly sensitive urine or serum pregnancy test to confirm absence of pregnancy
- Assess AEs until 30 calendar days (+/- 2 days) after last study drug intake
- Review concomitant medications since the last study visit
- Collect all unused study drug
- Assess study drug dosing compliance
- Biomarker analysis (if consent obtained by patient): Peripheral blood samples will be collected and stored for potential molecular studies (Section 6.4)

5.2 In-Study Long-term Follow-Up

After patients permanently discontinue pracinostat/azacitidine or placebo/azacitidine, they will be followed every 3 months (±1 month) from the date when study drug was last administered until the end of the study. The following information will be obtained during these Follow-up contacts:

- Collect any new AML treatment
- Collect any evidence of disease progression
- Assess survival status

- When there is a suspicion of disease progression, a bone marrow evaluation is required to confirm disease progression

Every effort must be made to follow patients from the time of treatment discontinuation until death. Patients may be contacted during outpatient visits or by telephone.

5.3 Post-Study Observation Period

The Post-Study Observation Period is defined as the period starting from the end of the study (Section 3.2) for a maximum of 24 months.

Patients still on treatment at the end of the study may have the opportunity to continue to receive the study drug to which they were randomized, until the Sponsor informs the Investigators of the appropriate course of action, based on the study results.

5.3.1 Patients on treatment at the end of study

For patients still on treatment at the end of study the following information will be collected in a dedicated CRF:

- End of treatment (date of last study drug administration)
- Any new AML treatment
- Any evidence of disease progression
- Serious Adverse Reactions (SARs) and follow-up information of SARs
- Death

5.3.2 After discontinuation of the treatment each patient enters in the post-study long-term follow-up as described below.Post-study long-term follow-up

After the end of the study, patients on post-study long-term follow-up will continue to be followed every 3 months (±1 month). The following information will be obtained during these Follow-up contacts and recorded in a dedicated CRF:

- Any new AML treatment
- Any evidence of disease progression
- Survival status
- Serious Adverse Reactions (SARs) and follow-up information of SARs

Every effort must be made to follow patients from the end of the study until Death. Patients may be contacted during outpatient visits or by telephone.

Results of this post-study observation period will be described in a separate study report.

6 METHODS OF ASSESSMENT AND ENDPOINTS

6.1 Efficacy Assessments

6.1.1 Bone Marrow Aspirate/biopsy

Bone marrow aspirate/biopsy sample will be collected for

- Morphologic diagnosis of AML at screening and evaluation of morphologic response to therapy
- Classical cytogenetic analysis - karyotyping (central evaluation) to assess cytogenetic risk category and allow stratification by cytogenetic risk factor (intermediate vs. unfavorable) at randomization and to evaluate cytogenetic response to therapy in patients with abnormal cytogenetics at screening. If the screening bone marrow aspirate sample for central cytogenetic analysis has been submitted but is the only pending result to confirm patient eligibility and a local cytogenetic analysis (karyotyping) has been already performed as per clinical routine within 30 days prior to the ICF signature, then the local result will be considered acceptable to enroll the patient.
- MRD evaluation by MFC
- Biobanking for mutational analysis
- If no bone marrow blood can be aspirated at screening ("dry tap", even at repeated attempts) the patient will be considered a screen failure.

Evaluation of bone marrow aspirate is to be performed at screening (a morphologic evaluation of bone marrow already performed within 30 days prior to the ICF signature will be accepted as screening evaluation) and then at the end of every even cycle (between Day 21 and 26), to evaluate the disease response to therapy at the beginning of each odd cycle. Response evaluation will be performed upon investigator's assessment, according to IWG criteria. A bone marrow biopsy is only required in case of dry tap for the pathology interpretation of response, including bone marrow blasts.

A local anesthetic (i.e., lidocaine, equimolar 50% nitrous oxide gas) may be applied to the skin and to the bone to numb the area where the aspirate/biopsy will be performed, preventing or reducing the pain associated to the procedure.

Morphologic response evaluation assessment will be required until a complete response is achieved and confirmed after 2 further cycles of treatment. At subsequent cycles, bone marrow evaluation is no longer required, unless there is a suspicion of disease progression or relapse from CR.

Classical Cytogenetics (karyotyping), with analysis of preferably 20 metaphases, is to be performed only if the screening cytogenetic test result was abnormal. After the patient has achieved a cytogenetic complete remission, the cytogenetic evaluation is no longer required at subsequent cycles.

MRD evaluation by MFC will be performed only at screening and after 2 cycles from first CR.

A small quantity of bone marrow blood will be collected and stored for retrospective analysis of mutations of six genes known to have a prognostic impact in patients affected by AML: NPM1, FLT3, CEBPA, RUNX1, ASXL1, TP53 (Döhner, 2016). The biobanking for these mutational analyses will be mandatory for study inclusion.

6.1.2 RBC and platelet transfusions

Information regarding red blood cell and platelet transfusions is to be collected on a regular basis, specifically date of transfusion, type of transfusion (red blood cells or platelets).

6.1.3 Quality of Life Questionnaire

Quality of life will be evaluated using the EORTC QLQ-C30 questionnaire (Appendix K).

The questionnaire is to be administered to the patients during the first visit of each odd cycle. Data of the questionnaire are to be reported in the eCRF.

6.2 Safety Assessments

Safety will be assessed primarily by means of adverse events (AEs) collection and reporting. See Section 8 below for specific definitions.

Additionally to the adverse events reporting, other safety assessments will include:

- Physical examination (PE)
- Vital signs
- 12-lead electrocardiogram (ECG)
- Laboratory tests (hematology, blood chemistry)

6.2.1 Physical Examination

A complete PE will be performed at Screening and during the Drug Holiday Commencement Visit. This evaluation will include an examination of general appearance, head, eyes, ears, nose, throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal and neurological.

A limited physical examination, covering general appearance, cardiovascular, lungs and abdomen body systems, will be performed at Day 1 of each cycle to assess any changes that may have occurred since the last examination.

Information about the physical examination will be recorded in the source documentation at the site. Any abnormalities will be recorded in the eCRF. Clinically significant findings/illnesses, reported after the first complete PE and which meet the definition of an AE, must be recorded in the eCRF as an AE.

6.2.2 Vital Signs

Vital signs assessments will include: pulse rate, systolic and diastolic blood pressure, body temperature, body weight, and height (at screening only).

Pulse rate, systolic and diastolic blood pressure will be measured after the patient has been in the sitting or in semi-supine position for at least 5 minutes. Measurements are done at Screening, on Day 1 of Cycle 1 (predose and 90 ±30 minutes postdose), on Day 15 of Cycle 1 (90 ±30 minutes postdose) on Day 1 of Cycle 2 (predose and 90 ±30 minutes postdose), at any time during the visit between Day 21 and Day 26 of Cycle 2 and 90 ±30 minutes postdose on Day 1 of all subsequent Cycles. Additionally these parameters are measured also during Drug Holiday Commencement and Follow-up Visits, as well as at End of Treatment Visit.

Body temperature is measured at Screening, on Day 1 of Cycle 1 (predose), on Day 15 of Cycle 1, on Day 1 of all subsequent Cycles (predose), as well as during Drug Holiday Commencement and Follow-up Visits, and at End of Treatment Visit.

Body weight is measured at Screening, on Day 1 of all Cycles, as well as during Drug Holiday Commencement and Follow-up Visits, and at End of Treatment Visit.

6.2.3 12-lead ECG

Twelve-lead ECGs will be recorded for each patient as triplicates or as single 12-lead ECG, as indicated in Section 5.1.

All ECGs will be recorded after the patient has been in sitting or in semi-supine position for at least 5 minutes. Triplicate ECGs are to be collected at a distance of 5±2 minutes between the ECGs.

Triplicate 12-lead ECGs are collected at Screening, on Day 1 of Cycle 1 (predose, 90 ±30 minutes and 6 hours ±30 minutes post pracinostat/placebo administration), on Day 2 of Cycle 1 (at 24 hours ± 1 hour post pracinostat/placebo administration), on Day 3 of Cycle 1 (at 48 hours ± 1 hour after the first pracinostat dose), on Day 15 of Cycle 1 (90 ±30 minutes post pracinostat/placebo administration), on Day 1 of Cycle 2 (predose and 90 ±30 minutes post pracinostat/placebo administration), and at Day 21-26 of Cycle 2 (at any time).

Single 12-lead ECGs are collected 90 ±30 minutes post pracinostat/placebo administration on Day 1 of each subsequent Odd cycle (i.e., Cycles 3, 5, 7 …).

Each ECG has to be signed and dated by the Investigator and evaluated as normal/abnormal. Abnormal clinically significant values detected at screening are not considered as AEs, but need to be reported in the medical history page, as appropriate. Clinically significant findings reported after screening have to be entered in the eCRF as AEs.

A digitally recorded ECG will be transmitted from the site to a central reading facility, where ECG interpretations will be timely performed by a cardiologist blinded to the treatment received by patients. ECG interpretation scheme will include the analysis of the morphology, rhythm, conduction, heart rate, ST segment, PR, QRS, QT and QTc intervals, T waves, U waves and the presence or absence of any pathological changes. After review, the Investigator must sign and date each ECG report received from the central reading facility.

The Investigator will receive more detailed information regarding the ECG recording and assessment procedures in a separate manual.

6.2.4 Laboratory Assessments

Blood samples will be collected at the relevant visits as indicated in Section 5.1 (i.e., Screening, Day 15 of Cycle 1, Day 1 of Cycle 2, ,between Day 21-26 of Cycle 2 and all subsequent cycles and End of Treatment Visit). All blood samples will be sent to the central laboratory for analysis (for details regarding processing and shipment please refer to the separate manual).

Females of childbearing potential will perform serum beta-hCG pregnancy tests at screening visit, Day 1 of Cycle 2, between Day 21 and Day 26 of Cycle 2 and all subsequent cycles and End of Treatment Visit. Pregnancy will be re-evaluated by urine pregnancy test (dipstick done locally at study site) predose on Day 1 of Cycle 1.

The following parameters will be analyzed for each sample:

Hematology panel: complete blood count (CBC): hematocrit, hemoglobin, erythrocytes (RBC), platelets, leukocytes (WBC) with differential (neutrophils, lymphocytes, basophils, eosinophils, monocytes and blasts).

HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc, HCV serology (anti-HCV) and HIV will be required only at screening.

HIV will be performed based on local regulation at local laboratory. HIV test already performed within 30 days prior to the ICF signature will be accepted as screening evaluation.

Blood chemistry panel: glucose, blood urea nitrogen/urea, creatinine, creatinine clearance (derived from blood creatinine value by Cockcroft formula), sodium, potassium, chloride, calcium, phosphorus, magnesium, bicarbonate /carbon dioxide (CO2), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, uric acid, albumin, and lactic acid dehydrogenase (LDH)

Coagulation panel: PT, INR, PTT, fibrinogen, D dimer

After review of the laboratory data, the Investigator must sign and date each laboratory report. The laboratory will provide normal reference ranges on the laboratory results report and will flag all abnormal values. The Investigator will assess the clinical relevance of values outside the normal range and repeat, if needed, any clinically significant abnormal laboratory test.

Only clinically significant abnormal laboratory values should be recorded and reported as AEs or SAEs depending on the evaluation performed by the Investigator. Abnormal clinically significant laboratory values detected at screening are not considered AE, but the underline disease needs to be reported in the medical history page, as appropriate. Whenever possible, the etiology of the abnormality should be identified and the diagnosis should be recorded as an AE.

6.3 PK Assessments

6.3.1 Pracinostat Population PK Assessments

Sparse blood samples will be collected in Cycle 1 on Days 1, 2, 3 and 15 in all study patients (except for patients participating in the AZA/pracinostat PK sub-study; refer to Section 6.3.2) to characterize the pracinostat population PK and assess the effect of drug exposure on safety and efficacy.

The following population PK samples are to be collected post pracinostat/placebo administration:

- 30 minutes ± 15 minutes
- 3 hours ± 30 minutes
- 6 hours ± 30 minutes
- 24 hours ± 1 hour (before AZA administration)
- 48 hours ± 2 hours (before next pracinostat/placebo dose intake)
- Day 15 (any time within 24 h after pracinostat/placebo dosing for the day)

The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution containing 20IU/mL Na-heparin. The first 1.0-1.5 mL of blood will be discarded to eliminate the heparin solution before any sample collection.

Blood samples of 1.5 mL will be collected into tubes containing K_2EDTA as anticoagulant.

Plasma will be obtained by centrifugation in a refrigerated centrifuge and divided in two Eppendorf tubes. Each tube will be filled with at least 150 µL of plasma for the assay of pracinostat and its metabolites (sample and back-up sample).

The samples will be stored frozen and sent to the central laboratory for analysis. The validated LC-MS/MS analytical method requires 50 µL of plasma for the assay of pracinostat and its metabolites.

Please refer to the laboratory manual for more detailed information.

6.3.2 AZA/Pracinostat PK sub-study (IN SELECTED SITES ONLY): Assessment of the possible drug interaction of Pracinostat on the PK of Azacitidine

The azacitidine PK in individual patients with/without the concomitant administration of pracinostat will be studied in the two groups of patients according to a dense blood sampling scheme and non-compartmental analysis (NCA). Each group will be composed of at least 12 subjects. The possible interaction of pracinostat on the PK of azacitidine will be assessed by comparing the descriptive statistics of PK parameters of azacitidine in the two groups. The sub-study will be performed at selected sites and only in patients administered subcutaneous AZA. This approach will be preferred over a population PK approach because of the known instability of azacitidine in blood and plasma, which

makes the correct and reliable application of a strict sample handling procedure at each clinical site difficult.

Blood samples will be collected at the following time points on Cycle 1 Day 1 **after** start of AZA administration:

- 15 minutes ± 2 minutes
- 30 minutes ± 2 minutes
- 1 hour ± 5 minutes
- 2 hours ± 5 minutes
- 3 hours ± 5 minutes
- 4 hours ± 5 minutes
- 6 hours ± 30 minutes
- 8 hours ± 30 minutes (optional sampling)

On Cycle 1 Day 2 before start of AZA administration:

- 24 hours ± 1 hour

The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution containing 20IU/mL Na-heparin. The first 1.0-1.5 mL of blood will be discarded to eliminate the heparin solution before any sample collection.

Blood samples of about 4 mL will be collected for each timepoint (until 24 hours ± 1 hour) in two tubes containing K_2EDTA as anticoagulant:

- One tube containing 2 mL of blood will be processed for the assay of Azacitidine and it must be stabilized by adding, **immediately after collection**, the appropriate stabilizer tetrahydrouridine (THU). After centrifugation, the plasma obtained will be divided in two tubes to be filled in with at least 500 µL of plasma each (sample and back-up sample).
- The second tube containing 2 mL of blood will be processed for the assay of Pracinostat and its metabolites. After centrifugation, the plasma obtained will be divided in two tubes to be filled in with at least 150 µL of plasma each (sample and back-up sample).

Only for the assay of Pracinostat and its metabolites, two additional blood samples of 1.5 mL each will be collected into tubes containing K_2EDTA as anticoagulant at the following time points on Cycle 1:

- Day 3: 48 hours ± 2 hours (before next pracinostat/placebo dose intake)
- Day 15: (any time within 24 h after pracinostat/placebo dosing for the day)

Plasma obtained by refrigerated centrifugation will be divided in two Eppendorf tubes. Each tube will be filled in with at least 150 µL of plasma (sample and back-up sample).

The samples will be immediately stored frozen at -20°C (pracinostat/placebo samples) or at -70°C (azacitidine samples) and sent to the central laboratory for analysis.

The validated LC-MS/MS analytical methods require 200 µL of plasma for the assay of azacitidine and 50 µL of plasma for the assay of pracinostat and SB991.

Please refer to the laboratory manual for more detailed information.

6.4 Biomarker Analysis (Optional)

The purpose of this exploratory study is to assess the presence, type, and frequency of AML-related molecular mutations in this patient population and whether there is an association between specific mutations and disease outcome with the study therapy.

The planned biomarker analyses involve the analysis of protein and nucleic acids (i.e., RNA and/or DNA). Biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e., mode of action or safety of the drug) may be measured, based on newly emerging data from other ongoing trials of these investigational drugs and/or literature data. However, the study sponsor reserves the right not to conduct all or part of the biomarker analysis. Data from this biomarker analysis may be correlated with various other data obtained in this study (e.g., clinical efficacy, pharmacokinetics, toxicity).

Peripheral blood samples and/or aspirate bone marrow samples will be collected and stored for potential molecular studies at screening, between day 21 and day 26 of every even cycle and at End of Treatment visit.

Specimens to study AML-related molecular mutations will be collected from patients who give specific consent to participate in this optional research. The Informed Consent Form will contain a separate section that addresses participation in the molecular mutation assessments. The Investigator or authorized designee will explain to each patient the objectives, methods and potential hazards of participation in this research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement for this purpose.

Dates of consent should be recorded in the associate page of eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Collection and submission of these samples is contingent upon the review and approval of the exploratory research portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee and, if applicable, appropriate regulatory body. If a site is not granted approval for these assessments, this section of the protocol will not be applicable at that site.

6.5 Efficacy Endpoints

6.5.1 Primary Endpoint

The primary efficacy endpoint is the overall survival (OS) measured as the time from randomization until death from any cause.

6.5.2 Secondary Endpoints

6.5.2.1 Morphologic Complete Remission (CR) rate

6.5.2.2 The CR rate is the proportion of patients who achieve a morphologic CR according to the IWG response criteria (Appendix F) in the absence of interceding therapies, including salvage treatments and HSCT, within the study period.Transfusion Independence (TI)

Transfusion independence rate is defined as the proportion of patients who achieve eight weeks or longer with neither red blood cell (RBC) nor platelet (PLT) transfusions during the study period [Fenaux, 2009; Silverman , 2006].

6.5.2.3 Complete Remission without minimal residual disease (CR_{MRD-}) rate

The CR_{MRD-} rate is the proportion of patients who achieve a CR with MRD negativity by multi-color flow cytometry, according to the IWG response criteria (Appendix F) within the study period.

6.5.2.4 Cytogenetic Complete Remission (CRc) rate

The CRc rate is the proportion of patients who achieve a reversion to a normal karyotype at CR (Appendix F) within the study period. This endpoint applies only to patients with abnormal cytogenetics at enrollment.

6.5.3 Exploratory Endpoints

6.5.3.1 Composite Complete Remission (cCR) rate

Composite complete remission (cCR) rate is the proportion of patients who achieve either a disease response of CR, CRi or MLFS (i.e., cCR = CR + CRi + MLFS) within the study period, (Appendix F).

6.5.3.2 Relapse Free Survival (RFS)

RFS is defined as the time from the date of achievement of CR or CRi until the date of relapse (progression) or death from any cause, whichever occurs first. RFS is only defined for patients who achieve a CR or CRi.

6.5.3.3 Progression Free Survival (PFS)

PFS is defined as the time from the date of randomization until the date of relapse (progression) or death from any cause, whichever occurs first.

6.5.3.4 Duration of Morphologic Complete Remission

Duration of Morphologic Complete Remission is defined as the time from the date of achievement of CR until the date of relapse (progression). Duration of CR is only defined for patients who achieve CR.

6.5.3.5 Duration of Composite Complete Remission

Duration of cCR response is the time from the date of achievement of either CR, CRi or MLFS (F) until the date of relapse (progression). Duration of cCR is only defined for patients who achieve a cCR.

6.5.3.6 Time to CR

Time to CR is defined as the time from the date of randomization until the date of CR in the absence of interceding therapies, including salvage treatments and HSCT.

6.5.3.7 Morphologic Complete Remission (CR) within 6 cycles rate

Morphologic complete remission (CR) within 6 cycles rate is defined as the proportion of patients who achieve CR in the absence of interceding therapies, including salvage treatments and HSCT, within 6 treatment cycles.

6.5.3.8 Quality of Life

Computation of the global health status and of selected functional scales and symptom scales from the EORTC QLQ-C30 questionnaire will be performed and their change from baseline over the study period will constitute the endpoints.

6.6 PK Endpoints

- To characterize the pharmacokinetics (PK) of pracinostat and its main metabolites in AML patients by a population pharmacokinetic approach
- To characterize demographic, physiopathological and therapeutic covariates that may influence pracinostat PK parameters and their interindividual variability
- To characterize the pracinostat exposure-response relationship for safety and efficacy endpoints (PK/PD)
- To assess the possible drug interaction of Pracinostat on the PK of AZA in AML patients by comparing the descriptive statistics of PK parameters of azacitidine in the two groups

7 DISCONTINUATION FROM STUDY TREATMENT PHASE OF THE STUDY

7.1 Patient Treatment Discontinuation

If patients experience any of the following, then they must discontinue from the study treatment phase of the study:

- Documented disease progression or relapse after CR by the International Working Group (IWG) criteria (Appendix F).
- Lack of clinical benefit. Clinical responses may require at least 6 courses of study treatment. Therefore, discussion with the Medical Monitor is recommended prior to discontinuation of a patient on the basis of lack of clinical benefit.
- Irreversible or intolerable toxicity or abnormal and clinically significant laboratory findings that cannot be managed with study treatment dose reduction or interruption.
- A patient's request to discontinue treatment for any reason. If a patient requests discontinuation from study treatment due to an AE, the primary reason for discontinuation should be the adverse event.
- Non-compliance with study treatment or study-related assessments that compromise the proper evaluation of the patient's safety
- Lost to follow-up.
- Sponsor decision: The Sponsor reserves the right to discontinue the study at any time for either clinical or administrative reasons. This decision will impact patients in the treatment and in the Long-term Follow-up phases of the study.
- Pregnancy.

Upon study treatment discontinuation, assessments of the End of Treatment Visit must be completed (refer to Section 5.1.14). Discontinued patients will enter the Long-term Follow-up phase of the study (refer to Section 5.2). Every attempt must be made to contact the patient prior to assigning the patient a lost to follow-up status. For patients who are lost to follow-up, no Long-term Follow-up is expected.

7.2 Patient Withdrawal

Patients have the right to voluntarily withdraw from the study at any time and for any reason. In addition, a patient's participation in the study may be discontinued at any time at the discretion of the Investigator. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Death
- Lost to Follow-Up
- Patient withdrawal of consent at any time during the patient's study participation, including during the Long-term Follow-up phase of the study.

Every effort should be made to obtain survival information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented

in the patient's study records and in the eCRF. Patients who withdraw from the study will not be replaced.

7.3 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Non-compliance with ICH-GCP guidelines
- Inadequate rate of patient recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

7.4 Study Termination

Study termination is defined as the time when all study treatments, study related-assessments, and study data collection are completed. Upon termination of the study, the Sponsor or designee will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations and the Study Manual.

The Sponsor reserves the right to temporarily suspend or terminate the study at any time for reasons including, but not limited to, safety issues or ethical reasons. The Sponsor or designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action, when applicable. Where required by applicable regulations, the Investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Ethics Committee (EC).

8 SAFETY

8.1 Safety Parameters and Definitions

Safety assessments will consist of evaluating and recording AEs, including serious adverse events (SAEs); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs, and physical examinations.

8.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of a drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Adverse reactions are defined as a subset of all adverse events for which there is reasonable possibility that the drug caused the event.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study.

8.1.1.1 Suspected Adverse Reaction

Suspected adverse reactions are the subset of all AEs for which there is a reasonable possibility that the drug caused the event. For the purposes of US Investigational New Drug (IND) safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

8.1.1.2 Life-threatening AE or Life-Threatening Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

8.1.1.3 Serious AE or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘serious’’ if any of the following criteria is met:

- Death, including death that appear unrelated to the study treatment
- Life-threatening AE
- Inpatient hospitalization or prolongation of an existing hospitalization, excluding the following scenarios:
    i. Emergency room visit or hospital visit without official admission

ii. Prolongation due to management or progression of the underlying disease

iii. Hospitalization for a pre-existing condition, provided that any of the following criteria are met:

1. The hospitalization was planned
2. Hospitalization to accommodate study treatment administration or required study procedures
3. Hospitalization due to disease progression

- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.1.4 Unexpected AE or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "unexpected" if it is not reported in nature, severity or incidence in the current version of the pracinostat IB (Section 7. Appendix).

8.1.1.5 Treatment-Emergent Adverse Event

A TEAE is an adverse event that emerges, or a pre-existing adverse event that worsens in severity, any time after the patient receives Dose 1 of study drug (pracinostat/placebo) through the end of the AE reporting period. AEs with onset before the patient receives Dose 1 of study drug are considered as pre-treatment AEs. AEs with onset after the end of the reporting period (if any) are considered as post-treatment AEs.

Laboratory tests, vital signs, and ECG abnormalities will be reported as AEs only if the event is considered clinically significant or leads to medical intervention (e.g., additional concomitant medication or procedures, discontinuation of study drug). Refer to Section 8.2.5.3 for details.

8.2 Adverse Event Reporting

All adverse events occurring from the informed consent signature until 30 calendar days after last study drug (pracinostat/placebo) intake, or until the initiation of new therapy for AML, whichever occurs first, are to be recorded on the appropriate eCRF section.

Every effort must be made by the Investigator to categorize each adverse event according to its severity and its relationship to the study treatment (study drug and/or azacitidine).

All AEs will be followed until symptom resolution or until the condition stabilizes, unless, in the Investigator's opinion, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease or unless the patient is lost to follow-up.

Whenever a change in the severity of an AE (such as a worsening) has occurred, a follow up of the initial AE should be entered in the eCRF reporting the new severity.

Outcome of ongoing serious and non-serious AEs will be reported in eCRF until the end of the reporting period as above defined. All non-resolved serious and non-serious AEs beyond such date will be recorded in eCRF as "ongoing" without further follow-up.

8.2.1 Serious Adverse Event (SAE)

Any SAE, irrespective of the relationship to study treatment, must be reported by the Investigator to CRO. Within 24 hours of the study site staff becoming aware of any SAE, the Investigator or the Investigator's designee must complete the eCRF with all necessary information. Any accompanying source documents (hospital records, autopsy report, etc.) should be faxed or e-mailed (as PDFs) at the following 24-hours contact information:

Email: Helsinn.safety@clinipace.com

Fax: +49 6196 7709 112

SAEs should be collected from the informed consent signature until 30 calendar days after discontinuation or completion of study treatment, or until the initiation of new therapy for AML, whichever occurs first, and followed until resolution.

"Disease progression" or "relapse from remission"as such, should not be reported as SAEs.
"Death" is an outcome and should not be reported as an SAE, unless the cause leading to death is unknown. When recording an SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single serious adverse event term.

The Investigator must immediately (within 24 hours) report follow-up information for initial events to Clinipace and the Sponsor as described above. Follow-up information can include but is not limited to the following significant information:

- New signs or symptoms or a change in the diagnosis
- Clinically significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting of initial and follow-up SAEs to their Institutional Review Board (IRB)/ Ethics Committee (EC) according to their own interpretations of the regulations and their own institutional policies.

The Sponsor/ designee is responsible for SAE reporting to the Regulatory Authorities where the study is conducted, according to reporting requirements as per local regulatory rules.

8.2.2 Pregnancies

Male patients and female patients who are of childbearing potential must use an effective contraceptive/birth control while participating on study. Pregnancies in female patients or female partners of male patients must be notified by the Investigator to the Sponsor/designee within 24 hours from knowledge of the pregnancy. If a female patient becomes pregnant, study treatment must be immediately discontinued until delivery. The Investigator should obtain informed consent from the patient or from the patient's partner allowing the Investigator to obtain information regarding the pregnancy and its outcome. If the patient's partner provides informed consent, the Investigator should follow the pregnancy until outcome and report this outcome to the Sponsor/designee.

An induced abortion or a spontaneous abortion is considered to be a SAE and should be reported in the same timeframe and in the same format as all other SAEs.

8.2.3 Adverse Event Severity

All AEs will be graded for severity using the NCI CTCAE v4.03.

If an AE is not listed in the NCI CTCAE v4.03, refer to Table 3 for guidance on grading of AE severity.

Table 3: Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.03), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event, per the definition of serious adverse event in Section 8.1.1.3.

8.2.4 Adverse Event Causal Relationship to study treatment

The Investigator's assessment of causality must be provided for all AEs whether serious or non-serious. Investigators should use their knowledge of their patients, the circumstances surrounding the event, and an evaluation of any potential alternative cause to determine whether or not an AE is considered to be related to the pracinostat, azacitidine, or both, indicating "yes" or "no" accordingly: see Table 4.

Table 4: Adverse Event Causal Attribution Guidance

Yes, Related	A reaction that follows a plausible temporal sequence from administration of the study treatment and cannot be explained by the subject's clinical state, intercurrent illness, or concomitant therapies, and/or follows a known response pattern to the suspected study treatment, and/or abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.
No, not Related	The adverse event has no plausible temporal relationship to administration of the study treatment; and/or is related to other etiologies such as concomitant treatments or patient's concurrent or pre-existing clinical state.

8.2.5 Procedures for Recording of Adverse Events

8.2.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded for that Adverse Event rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice and elevated transaminases).

8.2.5.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. The initial severity (intensity) of the event will be recorded at the time the event is first reported. Changes over time in toxicity grade should be recorded as follow up of the initial event.

8.2.5.3 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. Laboratory test results (including cytopenias) which are expected by the Investigator should not be reported as an AE unless:

- The event is accompanied by clinically significant symptoms which are new or worsened from baseline.
- Result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Result in a medical intervention (e.g., blood transfusion for anemia, potassium supplementation for hypokalemia) or a change in concomitant therapy.

- The event is clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE.

8.2.6 Adverse Events of Special Interest

Adverse events of Special Interest are defined as pre-specified AEs, serious and non-serious, under ongoing monitoring by the Sponsor.

No specific reporting timelines or other activities are required by the Investigator in addition to the normal AE reporting practices as described in the above sections for the followings AE of special interest:

- Supraventricular arrhythmias
- Sepsis, septic shock, grade ≥3 lung infection (pneumonia)
- Any infection leading to death
- Grade ≥3 anemia, neutropenia, febrile neutropenia and thrombocytopenia
- Grade ≥3 haemorrhage

8.2.6.1 QTc prolongation

Any QTc prolongation ≥ 500 ms and/or > 60 ms change from baseline, irrespective of the relationship to study treatment, must be always reported as an AE. The Investigator or the Investigator's designee must complete the AE pages of eCRF with all necessary information and any accompanying source documents (hospital records, ECG report, etc.) should be faxed or e-mailed (as PDFs) at the following contacts:

Email: Helsinn.safety@clinipace.com

Fax: +49 6196 7709 112

8.2.6.2 Adverse Events Associated with an Overdose

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the protocol. An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All overdoses should be recorded, independently from an association with AEs.

All AEs associated with an overdose or incorrect administration of study treatment should be recorded.

If an overdose results in an SAE, it must be reported to the Sponsor as an SAE within 24 hours of identifying the event. Currently, there are no safety data related to pracinostat overdose. If overdose is suspected, administration of study drug should be stopped and general supportive measures instituted.

8.2.7 Patient Unblinding For Safety Reasons

Unblinding of study treatment (i.e., pracinostat or placebo) for a specific patient will only be permitted in the event of a medical emergency that would require the investigator to be aware of the treatment allocation prior to the end of the study. For any study treatment unblinding, the reason must be documented in the patient's medical record. Treatment identification information should be kept confidential.

8.2.7.1 Unblinding Procedure

The Investigator has the possibility to unblind the study treatment in case of an emergency situation, when he/she considers essential to know what treatment the patient is receiving. To proceed with the unblinding procedure, he/she is allowed to access TEMPO™ system (available 24 hours 7 days coverage), select the patient identifier and choose the "Unblinding of study treatment" Form in the "Subject management" section. After confirmation of the request, the treatment regimen assigned to patient at the time of randomization will be shown together with the list of identifiers of the kits assigned. A notification email informing that the code has been broken, but not reporting the treatment assigned, is sent to the person performing the unblinding and to the Sponsor. If the code is broken by Investigator, the patient should be discontinued permanently from treatment and he/she will enter the long-term follow-up period.

When an event might be a Suspected Unexpected Serious Adverse Reaction (SUSAR) the blind should be broken by the Sponsor for pharmacovigilance reporting purposes only for that specific subject. Unblinding information should only be accessible to those who need to be involved in the safety reporting to Regulatory Authorities, while the blind should be maintained for all other persons responsible for the ongoing conduct of the study. The patient will not be withdrawn from the study in case of unblinding by the Sponsor's Drug Safety Department for pharmacovigilance reporting purposes.

8.3 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established for this study to serve in an advisory capacity to the Sponsor. The IDMC will be primarily responsible for assessing emerging safety data on an ongoing basis as well as a one-time evaluation of an interim efficacy analysis and will recommend whether the study should be stopped based on 1) reaching the pre-specified criterion for superiority or the pre-specified criterion for futility and 2) the overall risk-to-benefit assessment.

The IDMC will consist of at least two AML disease experts and a biostatistician (none of them being employees of the Sponsor or of the CRO or investigators in the study). The IDMC will regularly review cumulative safety data and make recommendations, if necessary, to the Sponsor relating to the selection, recruitment, and retention of patients; patient management; improving adherence to protocol-specified treatments and assessments; and the procedures for data management and quality control. The IDMC may be unblinded for some or all patients according to the conditions established in the IDMC charter.

The scope and details of obligations of the IDMC members and operational details of the committee will also be described in the IDMC Charter to be finalized before the start of patient enrollment.

9 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

9.1 Statistical Design

This is a Phase III, global, double-blind, randomized, placebo-controlled study comparing the efficacy and safety of pracinostat or placebo in combination with azacitidine in patients with previously untreated AML who are aged ≥ 18 years. This is an event-driven study and an interim analysis for both futility and superiority will be performed at 2/3 of information (260/390 events).

The primary efficacy endpoint is overall survival (OS) in the intent-to-treat (ITT) patient set using the log-rank test stratified by cytogenetic risk and ECOG. The null and alternative hypotheses to be tested for OS distribution, assuming proportional hazards, are:

H_0: HR ≥1

H_1: HR < 1

where HR is the hazard ratio of the pracinostat group over the placebo group.

Hazard Ratio equal to 1 is used as H_0 for sample size calculations.

Secondary endpoints will be tested according to a fixed sequence method. If the primary endpoint is statistically significant, then the first secondary endpoint (according to the predefined list) will be tested, and so on for the other three secondary endpoints. When the sequence stops for a non-significant test the following tests will be downgraded to exploratory.

9.2 Randomization and Stratification

This study will employ a 1:1 randomization. Patients will be stratified based on the following factors:

- Cytogenetic risk category (intermediate vs. unfavorable-risk)
- ECOG 0/1 vs. 2

Information on pracinostat + AZA (Phase 2 study MEI-004) suggests some factors as influencing the OS. This information was combined with information provided by current literature on AZA [Dombret, 2015] and the most influencing factors emerged as candidates chosen as stratification factors at randomization to guarantee a proper balance between treatments. In particular ECOG was selected as grade 2 is generally much less frequent than grades 0/1, while Cytogenetic risk was included as showing a large difference between intermediate and unfavorable risk.

If available, the central cytogenetic test result will be used to assess the cytogenetic risk category at randomization. If the central result is not available, the local result will be used.

Randomization will be conducted centrally via an IWRS.

9.3 Analysis Sets

The definitions of analysis sets are as follows:

1) All randomized (Intent-to-Treat; ITT) - This set will comprise all randomized patients, regardless if the patient was administered study drug. Patients will be assigned to treatment groups based on the randomized study drug assignment. This set will be the primary set analyzed for the primary efficacy endpoint (OS) and will be also used for the efficacy endpoint RFS and the analysis of durations of response (limited to patients with response), transfusion independence, for the analysis of the efficacy endpoints CR rate , CR_{MRD-} rate and for the exploratory endpoints.
2) Safety - This set will comprise all patients who received at least one dose of study drug (pracinostat/placebo). Patients will be assigned to treatment groups based on the actual drug received. This set will be the primary set analyzed for safety.
3) Per Protocol (PP) – This set will comprise patients who met all eligibility criteria and received randomized study treatment without substantial deviations or violations. This set will be the secondary set analyzed for the efficacy endpoint OS.
4) ITT-2– This set will comprise patients in the ITT set with abnormal cytogenetics at enrollment. This will be the primary set used for the analysis of the efficacy endpoint CRc rate.
5) Efficacy Evaluable 1 (EE-1) – This set will comprise patients in the ITT set who had a complete disease response assessment. A complete disease response assessment is defined as at least 1 post-baseline peripheral blood count determined and 1 post-baseline bone marrow assessment performed, with an Investigator response reported. A peripheral blood count is defined as an assessment of absolute neutrophil count (ANC), platelets and peripheral blasts. In addition, patients who discontinued due to progressive disease (per the Study Discontinuation form) without a complete disease response assessment will also be included in this Efficacy Evaluable Set. This will be the secondary set used for the analysis of the efficacy endpoints CR rate, CR_{MRD-} rate and cCR rate.
6) Efficacy Evaluable 2 (EE-2) –This Efficacy Evaluable Set will comprise all patients in the ITT-2 who had a complete disease response assessment. A complete disease response assessment is defined as at least 1 post-baseline peripheral blood count determined and 1 post-baseline bone marrow assessment performed, with an Investigator response reported. A peripheral blood count is defined as an assessment of absolute neutrophil count (ANC), platelets and peripheral blasts. In addition, patients who discontinued due to progressive disease (per the Study Discontinuation form) without a complete disease response assessment will also be included in this Efficacy Evaluable Set. This will be the secondary set used for the analysis of the efficacy endpoint CRc rate.

Detailed information on these and other sets will be provided in the Statistical Analysis Plan.

The PK analysis set(s) will be defined in the Statistical Analysis Plan (SAP) dedicated to the PK.

9.4 Procedures for Handling Missing, Unused and Spurious Data

All available efficacy and safety data will be included in the data listings and tabulations. Handling of missing data and imputation of values for missing data is presented, however further details will be given in the SAP.

Censoring rules for time-to-event endpoints (e.g., OS and RFS) are described in Section 9.7.

9.5 General Statistical Considerations

Continuous endpoints will be summarized using descriptive statistics, which will include the number of patients with a valid measurement (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. Time-to-event endpoints (in particular OS) will be analyzed using Kaplan-Meier product limit methods to estimate the survival distribution, median time-to-event with 95% confidence interval and survival probabilities at selected time points; numbers of patients at risk, patients with an event, patients censored at selected timepoints will be reported too.

For analyses of endpoints of a proportion of patients with disease response performed on the relevant ITT/EE set, the number of patients in the relevant ITT/EE set will be the denominator for the proportion.
A summary table including the best response obtained for each subject during study course will also be presented (number of patients and related percentage). Absence of interceding therapies, including salvage treatments and HSCT is requested for considering the response (CR, CRi, MLFS, PR, SD) in the analysis, otherwise the response will be considered as not evaluable.

The analysis sets will be the ITT and the EE-1 set. The corresponding ITT-2 and EE-2 sets will be the basis when CRc is considered.

The safety endpoints will be listed and/or summarized by relevant time points, as appropriate.

Unless specified otherwise, the baseline value for efficacy and safety variables is the last non-missing value before the first dose of study treatment. Data listings will be created to support each table and to present all data.

Unless otherwise specified, all statistical tests will be 1-sided and carried out at the 0.025 α level. Further details regarding the statistical analysis are contained in the following sections and in the SAP.

9.6 Study Population Data

Patient disposition will be summarized for all screened patients. The total number of patients for each defined analysis set will also be tabulated. The demographic and baseline characteristics will be summarized for the ITT, ITT-2 and Safety sets, as relevant. Study treatment exposure and duration will be summarized using descriptive statistics for the Safety set.

9.7 Efficacy Analyses

9.7.1 Primary Efficacy Analysis - Overall Survival

The primary efficacy endpoint is overall survival (OS) measured as the time from randomization until death from any cause.

OS time for patients alive or lost to follow-up at the time of analysis will be censored at the date when they were last known to be alive.

OS will not be censored at the time of subsequent AML therapy. Both interim and final OS analyses will be performed on the ITT set. Final analysis will take place after the required number of events (390 deaths) has occurred.

The primary OS analysis will be based on the log-rank test stratified by the factors used for randomization (cytogenetic risk and ECOG) at the overall one-sided alpha = 0.025 level of significance (specific alpha levels will be used for interim and final analysis). Log-rank stratified by cytogenetic risk obtained by central laboratory (when available) and ECOG at Day 1 Cycle 1, unstratified log-rank test and Cox PH model including factors used for randomization will be used as sensitivity analyses to support evidence of efficacy. Kaplan-Meier estimates of OS in each treatment group will be reported, both overall and within strata of patients. Estimates of median survival will be provided with two-sided 95% confidence intervals, along with the 25th and 75th percentiles, together with the HR estimates. The number of surviving patients, the number of deaths and the number of patients with censored values will be displayed as well.

Checks on the proportionality of hazards will be performed.

Censoring patterns will be examined between treatment groups. The effect of subsequent therapy on OS will be analyzed, including an analysis that compares OS in the treatment groups with censoring at the start date of the new regimen subsequent AML therapy. Other sensitivity analyses will be performed to assess the robustness of OS results, if relevant.

The primary OS analysis (stratified log-rank test) will be repeated for the PP set.

Further exploration of baseline/demographic factors of interest will be done by means of Cox PH model.

9.7.2 Secondary Efficacy Endpoints

The secondary efficacy outcome measures for this study are the following (the order is relevant to the sequence procedure for testing endpoints):

- CR rate Transfusion independence
- CR_{MRD-} rate
- CRc rate

9.7.2.1 Morphologic Complete Remission (CR) rate

The rate of CR is defined as the proportion of patients who achieve a morphologic CR according to the IWG response criteria (Appendix F) in the absence of interceding therapies, including salvage treatments and Hematopoietic Stem Cell Transplant (HSCT), within the study period. The proportions in the two treatment groups will be compared at a 1-sided alpha = 0.025 level of significance using the Cochran-Mantel-Haenszel test stratified for cytogenetic risk and ECOG PS (values at randomization). In addition, the two-sided 95% CI for the difference between the responder proportions in the two treatment groups will be provided, using the stratified Newcombe method.

The analysis will be primarily performed in the ITT set (patients for whom no efficacy assessment is available will be analyzed as not having CR) and then in the EE-1 set.

Unstratified analysis will be done for sensitivity purpose by means of likelihood ratio Chi square test.

9.7.2.2 Further exploration of baseline/demographic factors of interest could be done by means of logistic regression models.Transfusion Independence

The proportion of patients who showed transfusion independence will be summarized by study treatment and transfusion dependence at baseline. The proportion of patients who are transfusion independent (by both RBCs and platelets) during study will be compared between the two treatment groups by using the same methods as those used for the CR rate analysis. The analysis set will be the ITT set. Rules for imputing missing data will be defined in the SAP.

9.7.2.3 Complete Remission without minimal residual disease rate

The CR_{MRD-} rate is the proportion of patients who achieve a CR with MRD negativity by multi-color flow cytometry, according to the IWG response criteria (Appendix F) within the study period (details will be given in the SAP). Absence of interceding therapies, including salvage treatments and HSCT is requested for considering the response in the analysis (for both CR and MRD negativity). CR_{MRD}- rate will be analyzed on the ITT and EE-1 sets, using the same methods as those used for the CR rate analysis. Patients for whom no assessment with multi-color flow cytometry is available at the planned time points will be analyzed as not having reached CR_{MRD-}. However, patients from sites for which no assessment of MRD was possible for logistic reasons will be excluded from the ITT/EE-1 sets. Additional rules will be defined in the SAP.

9.7.2.4 Cytogenetic Complete Remission rate

The rate of Cytogenetic Complete Remission (CRc) is defined as the proportion of patients who achieve a reversion to normal karyotype at CR (Appendix F) within the study period. Absence of interceding therapies, including salvage treatments and HSCT is requested for considering the response in the analysis.

CRc rate will be analyzed on the ITT-2 set (as this endpoint applies only to patients with abnormal cytogenetics at enrollment). CRc rate will be analyzed using the same methods as those used for the CR rate analysis. The endpoint will also be analyzed in EE-2 set.

9.7.3 Exploratory Efficacy Outcome Measures

The exploratory efficacy outcome measures for this study are the following:

- cCR rate
- Relapse Free Survival (RFS)
- Progression Free Survival (PFS)
- Duration of Responses (CR, cCR)
- Time to CR
- CR within 6 cycles

9.7.3.1 Composite Complete Remission rate

Composite complete remission (cCR) rate is defined as the proportion of patients who achieve either a disease response of CR, CRi or MLFS (ie, cCR = CR + CRi + MLFS) within the study period (Appendix F). Absence of interceding therapies, including salvage treatments and HSCT is requested for considering the response in the analysis.

Composite CR rate will be analyzed on the ITT and the EE-1 sets. Composite CR rate will be analyzed using the same methods as those used for the CR rate analysis. Patients for whom no efficacy assessment is available will be analyzed as not having cCR when considering the ITT set.

9.7.3.2 Relapse-free Survival (RFS)

RFS is defined as the time from the date of achievement of CR or CRi until the date of relapse (progression), or death from any cause, whichever occurs first.

Censoring rules will include the following:

- Time to relapse (progression) will be censored at the date of the last assessment of patient status excluding relapse (progression). In case of no post-baseline disease assessments after CR, censoring will be at the date of CR/CRi.

RFS will be analyzed using the same methods as those used for OS (Kaplan Meier estimates and stratified log-rank test). In addition, possible RFS analyses based on other RFS censoring criteria (e.g. censoring at the date of start of a new therapy) will be specified in the SAP. The analysis set will be the ITT set limited to patients who achieve a CR/CRi in absence of interceding therapies, including salvage treatments and HSCT.

9.7.3.3 Progression-free Survival (PFS)

PFS is defined as the time from the date of randomization until the date of relapse (progression), or death from any cause, whichever occurs first.

Censoring rules will include the following:

- Time to relapse (progression) will be censored at the date of the last assessment of patient status excluding relapse (progression). In case of no disease assessments, censoring will be at the date of randomization.

PFS will be analyzed using the same methods as those used for OS (Kaplan Meier estimates and stratified log-rank test). In addition, possible PFS analyses based on other

PFS censoring criteria (e.g. censoring at the date of start of a new therapy) will be specified in the SAP. The analysis set will be the ITT set.

9.7.3.4 Duration of Morphologic complete Remission (CR)

Duration of CR is defined as the time from the date of achievement of CR until the date of relapse (progression). Kaplan-Meier methods will be used to estimate duration of response in each treatment group. Estimates of median duration will be provided with 95% confidence intervals, along with the 25th and 75th percentiles. Stratified log-rank test will be used to compare treatment groups.

Censoring rules will include the following:

- Time will be censored at the date of the last adequate assessment of patient status excluding relapse (progression). In case of no disease assessments after CR, censoring will be at the date of CR.

In addition, possible analyses based on other censoring criteria (e.g. censoring at the date of start of a new therapy) will be specified in the SAP. The analysis set will be the ITT set limited to patients who achieve a CR in absence of interceding therapies, including salvage treatments and HSCT.

9.7.3.5 Duration of Composite Complete Remission

Duration of cCR response is defined as the time from the date of achievement of either CR, CRi or MLFS until the date of relapse (progression), and will be analyzed as the duration of CR response.

Censoring rules will include the following:

- Time will be censored at the date of the last assessment of patient status excluding relapse. In case of no disease assessments after cCR, censoring will be at the date of cCR.

In addition, possible analyses based on other censoring criteria (e.g. censoring at the date of start of a new therapy) will be specified in the SAP. The analysis set will be the ITT set limiting to patients who achieve a cCR in absence of interceding therapies, including salvage treatments and HSCT.

9.7.3.6 Time to CR

Time to CR is defined as the time from the date of randomization until the date of CR in the absence of interceding therapies, including salvage treatments and HSCT. The analysis set will be the ITT set.

Time to CR will be censored at the date of the last assessment of patient status excluding CR in the case no CR occurred by time of analysis. In case of interceding therapies, PD or death, time to CR will be censored to the new AML treatment start date, PD assessment date or death date, respectively. Cumulative Incidence Function (CIF) will be computed as 1-Kaplan Meier curve and treatment groups will be compared by the log-rank test.

9.7.3.7 Morphologic Complete Remission (CR) within 6 cycles rate

Morphologic complete remission (CR) within 6 cycles rate is defined as the proportion of patients who achieve CR in the absence of interceding therapies, including salvage treatments and HSCT, within 6 treatment cycles. Analysis will be performed in the ITT set.

CR within 6 cycles rate will be analyzed using the same methods as those used for the CR rate analysis, limiting to the stratified analysis. Patients for whom no efficacy assessment is available will be analyzed as not having CR.

9.7.4 Subgroup Analyses

The primary endpoint of OS and the secondary endpoints of CR, CRc, CR_{MRD-} and transfusion independence will be also explored in subgroups based on stratification variables, as well as demographic and baseline patient characteristics. Details will be provided in the SAP.

In each defined subgroup, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint. These results will be considered exploratory because of the multiplicity issue and also smaller sample sizes that cannot be pre-specified. For subgroups without an adequate number of patients, the analyses will not be performed.

9.7.5 Quality of Life

Quality of life will be evaluated using the EORTC QLQ-C30 questionnaire.

Summary tables of absolute value and change from baseline at the different timepoints will be produced. Baseline will be the last value available before the first study drug administration on Day 1 of Cycle 1. The global health status and some of the functional scales or symptom scales, which will be defined in the SAP, will be analyzed.

9.7.6 Compliance to study treatment

Compliance with therapy (as defined in Section 4.8) will be summarized (number of patients compliant and percentage related to patients in the cycle) by cycle and by treatment group for pracinostat / placebo and for AZA.

Compliance over the whole study period will also be summarized. Specific rules to evaluate the overall compliance will be presented in the SAP.

9.8 Safety Analyses

Tolerability, safety and adverse events (AEs) will be assessed as follows:

- Incidence, nature, seriousness and severity of AEs and relationship to study treatment
- Discontinuations from drug or dose modifications due to AEs
- Values/findings and changes in vital signs, physical examinations (only listing of findings), electrocardiograms (ECGs) and laboratory values

9.8.1 Analysis of Adverse Events

The analyses of safety will be performed on the Safety set.

Terminology from the Medical Dictionary for Drug Regulatory Activities (MedDRA) will be used to assign System Organ Class (SOC) and Preferred Terms (PT) classification to AEs and diseases, based on the original terms entered on the CRFs.

The number and percentage of patients reporting TEAEs and study drug related TEAEs will be summarized by SOC and PT. Tables by worst CTCAE grade will be also produced. The number and percentage of patients reporting treatment-emergent SAEs and drug-related SAEs will be tabulated, as well as TEAEs leading to dose modification, to discontinuation of study treatment or leading to death. Pre-treatment AEs and post-treatment AEs (if any) will be listed. TEAEs of special interest will be presented also in specific summary table(s) and listing(s).

A by-patient AE (including treatment-emergent, pre-treatment and post-treatment (if any)) data listing including, but not limited to, verbatim term, PT, SOC, CTCAE grade, and relationship to study treatment will be provided. Deaths, other SAEs, including those leading to discontinuation of study treatment, will be listed.

The above described analyses will be performed overall. Further details and analysis by cycle will be described in the SAP.

In consideration of the study population, to better evaluate tolerability in elderly unfit subjects, part of the overall analysis described above will be performed also by age group, by ECOG class and by renal impairment category at baseline (based on glomerular filtration rate).

9.8.2 Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation for the Safety set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be summarized for the maximum and minimum post-treatment values and the values at the End of Treatment visit (or the last value obtained under treatment).

Abnormal clinical laboratory results will be graded according to NCI CTCAE version 4.03, if applicable, and the grade will be presented in a by-patient data listing. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results of Grade 3 or 4 will be listed.

9.8.3 Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation for the Safety set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be presented for the maximum and minimum post-treatment values and the values at the End of Treatment visit.

9.8.4 Electrocardiogram Analyses

Descriptive statistics will be provided for the central ECG measurements by scheduled time of evaluation for the Safety set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. For triplicate measurements the mean value will be used for analysis. ECG abnormalities will be graded according to the CTCAE criteria. The number and percentage of patients with QTcF interval values less than or equal to 450, between 451 and 480, between 481 and 500, as well as >500 ms will be tabulated and changes from baseline of less than 30 ms, 30-60 ms and >60 ms over all post treatment evaluations and by cycle will be summarized and described in relation to baseline values. ECG data will also be presented in the data listings.

9.9 Pharmacokinetic Analyses

The sparse concentration-time data collected for pracinostat and its metabolites will be analyzed by non-linear mixed effect modeling according to a population PK data analysis approach. The purpose of this analysis is to obtain exposure data in patients with AML, to characterize the PK parameters of pracinostat and its metabolites, and to identify relevant covariates affecting pracinostat exposure. In addition, exposure variables will be correlated to both efficacy and safety (AE) variables in a PK/PD analysis. The possible drug interaction of Pracinostat on the PK of AZA will be evaluated by comparing the descriptive statistics of PK parameters of azacitidine in the two groups. The analysis will be performed in the PK analysis set(s).

Additional details on the PK/PD methods and analysis will be provided in a dedicated SAP.

9.10 Health Economics Analysis

The analytical approach will be a cost efficacy analysis. The health economics analysis will be managed and conducted separately. Relevant patient data and analyses results will be presented in a separate report. Further details will be outlined in the Health Economics analysis plan.

9.11 Power and Sample Size Determination

This is an event-driven study. Sample size was computed for a group-sequential design with stopping rules for both futility and superiority (study-wise one-sided alpha level=0.025, power 0.90) with one interim analysis at 67% (2/3) of information and a final analysis. The error spending function is from the Gamma Family, using γ=-3.6 (similar to O'Brien Fleming) for superiority and γ=-5.5 (more conservative than O'Brien Fleming) for futility (non-binding). Proportionality of hazards is assumed. Assuming that median OS is 10.0 months in the Group B (placebo + AZA) the aim is to detect, by means of the log-rank test or equivalent, an increase to 14.0 months in Group A (pracinostat + AZA), i.e., a HR of 0.714. A total of 390 events (deaths) allows to meet a power requirement of at least 90% (actually 90.78%) at a study-wise one-sided significance level of 0.025.

Patient accrual is assumed to occur over a 30-month period. Assuming a non-constant accrual rate (100 patients during the first year and the remain patients during the following 1.5 years) and a 3% yearly drop-out rate, and considering that 500 patients will be recruited, it is expected that the post-recruitment follow-up period will take about 18 additional months to reach 390 events for final OS analysis.

Sample size calculations were made using SAS 9.2.

The overall event rate (blinded) will be constantly monitored. Before the expected recruitment end, the observed placebo hazard rate will be derived from the (blinded) overall observed hazard rate at that time, assuming a hazard ratio of 0.714. Based on the computed value the decision to adapt the sample size to enable study end within a reasonable amount of time from the end of recruitment might be taken. This procedure does not introduce bias and no statistical adjustments to preserve the study-wise alpha error are required.

A group-sequential procedure will be applied also to the secondary endpoints, adopting as the error spending function for superiority the Gamma Family, using γ=-3.6. Details on the procedure and power calculation for the secondary endpoints will be provided in the SAP.

9.12 Interim Analysis

One formal interim analysis on the primary endpoint, OS, is planned and will be assessed by the IDMC. The interim analysis is to be performed when 2/3 of the total number of events (260/390 deaths due to any cause) have occurred in the study, according to the group sequential testing design described in Section 9.11. Events should be reported to sponsor as soon as they become known to investigators and entered in the eCRF in a short time. As soon as the 260th event is reported to the sponsor, the set of 260 events will be considered as complete. This set of events will be submitted to final validation before analysis. Data emerged on a later time point (including events occurred earlier than the 260th event) will not be considered for the interim analysis. The same rule will be applied at the time of final analysis, if relevant. Further data will be considered in an addendum to the CSR.

Further details will be provided in the SAP and DMC Charter prior to the implementation of this interim analysis.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Compliance with Laws and Regulations

This global clinical study will be conducted in full conformance with the protocol, International Conference on Harmonization, Good Clinical Practice Guidelines E6 (ICH-GCP), and the principles of the Declaration of Helsinki, and the applicable laws and regulations of the country in which the research is conducted.

10.2 Institutional Review Boards and Ethics Committees

This protocol and any accompanying material that will be provided to the patient (e.g.; patient information sheet or patient diary) must be submitted to the IRB/EC and approval obtained prior to study start.

10.3 Informed Consent

The Investigator is responsible for obtaining written informed consent(s) from each study patient prior to conducting any study-related procedures. The Investigator must use the most current IRB/EC-approved consent form when obtaining consent.

At any time, all signed and dated Consent Forms must be available for Sponsor/designee verification.

10.4 Source Data Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigator's Study Files and patient clinical source documents. The Investigator must be able to provide the Sponsor/designee access to applicable source documents and reports.

10.5 Use of Computerized Systems

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document, if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

10.6 Quality control

To ensure compliance with GCP and all applicable regulatory requirements, site audits may be conducted at applicable participating sites. Regulatory agencies may also conduct regulatory site inspections of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, then the Investigator and institution agree to allow the auditor/inspector direct access to all

relevant documents. The Investigator and the site staff also agree to allocate adequate time to discuss findings and any relevant issues with the auditor/inspector.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for audits at any time by the Sponsor, its designees, and/or inspections by regulatory agencies. In signing this protocol, the Investigator understands and agrees to give access to the necessary documentation and files.

As applicable, the Sponsor or designee is responsible for implementing and maintaining quality control and quality assurance systems to ensure that this study is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.7 Retention of Records

All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may need to retain documents longer, if required by applicable regulatory requirements or if requested by the Sponsor. The Investigator must notify the Sponsor, in writing, prior to destroying any clinical study records.

Should Investigator wish to assign the study records to another party or move them to another location, the Investigator must notify the Sponsor/designee, in writing, prior to the transfer.

If the Investigator cannot guarantee this archiving requirement at the study site, for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor/designee to store these in sealed containers in an off-site storage location so that they can be returned to the Investigator in case of a regulatory inspection. Where source documents are required for the continued care of a patient, appropriate copies should be made for off-site storage.

10.8 Confidentiality

The Sponsor and the CRO must ensure that the Investigator keeps secret from third parties any confidential information disclosed or provided by the Sponsor and regarding the Sponsor and its study-related products. The Investigator agrees to use such information only to accomplish the present study tasks and not to use it for any other purposes without the prior written consent by the Sponsor. Prior to the study start-up, each Investigator as well as each subcontractor to be involved in the study should sign a confidentiality agreement with the CRO acting for and on behalf of the Sponsor.

10.9 Insurance

The Sponsor will obtain liability insurance, which covers health impairments resulting from drugs and/or substances/investigational products administered in the course of this study for which the patient has given his/her written Informed Consent.

11 PUBLICATION POLICY

Helsinn Healthcare SA is committed to public disclosure of research results that involve Helsinn Healthcare products. For Helsinn sponsored publications, the rules of the International Committee of Medical Journal Editors (ICMJE) will apply to all named authors. As a general rule, the Sponsor and the Investigator(s) agree that no publications presenting or discussing data and/or results from clinical trials sponsored by Helsinn Healthcare SA will take place until the participating center(s) has/have completed the study, the data have been interpreted, and the final report has been issued. The Sponsor is free to use the data collected in the sponsored study for the drug registration, world-wide scientific product documentation, and for publication. In general, the Sponsor has no objections if the Investigator publishes the results of the study obtained by the Investigator/Institution sponsored by Helsinn Healthcare SA; however, the Investigator is requested to provide the Sponsor with a copy of the manuscript for review before submitting it to the publisher, with a cover letter informing the Sponsor about the intention to publish the study results. Such a procedure is necessary to prevent premature disclosure of trade secrets or otherwise patent-protected material and is not intended as a restrictive measure concerning the study results or the opinions of the Investigators. After the review of the manuscript by the Sponsor, the Investigator will be provided with the Sponsor's comments, if any, and the opinion of the Sponsor regarding study results publication. The Investigator shall however consider the Sponsor's comments and proposed revisions. If requested by the Sponsor, the Investigator shall delay the presentation or publication of the study data in order to allow the Sponsor sufficient time to obtain Intellectual Property Protection. The Sponsor is entitled to include as authors of the publication all Sponsors' personnel who have contributed substantially to the theoretical or experimental activities.

Costs for publication must be regulated by written agreement between the parties. Data resulting from multicenter clinical trials have to be prepared and submitted prior to any publications from individual sites. For multicenter studies, the Investigators who will be quoted as authors of the publication(s) should be agreed upon with the Sponsor. If publication of the results of the study, either in part or in full, is prepared by the Sponsor, the agreed Investigator(s) will be asked in writing if he/she/they agree(s) to be listed as one of the authors of the publication. Answers should be sent in writing to the Sponsor within a reasonable time limit (30 days).

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13 APPENDICES

Appendix A: Schedule of Assessments

Assessments	**Screening[A]**		**Study Treatment Cycles (28 days)[B]**											**End of Treatment Visit**	**In-Study Long-Term FollowUp[V]**
Study Day	***Day -28 to -1***	***Day -8 to -1***	***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***	***Day 8***	***Day 9***	***Day 15***	***Day 21-26***	***30 Days (±2) after last study drug intake***	
Obtain Informed Consent [C]	X														
Randomization via IWRS			[X][D] C1 only												
Medical history, demographics	X		[X][D] C1 only												
Bone Marrow aspirate/biopsy and classic cytogenetic testing [E]	X												X even cycles		
Smoking status [F]	X														
Vital signs [G]	X		X									[X]	X C2 only	X	
Physical examination[H]	X		X												
ECOG Performance Status [I]	X		X											X	
Information on transfusion of RBC or platelets [J]			X										X even cycles		
Quality of Life Questionnaire [K]			X Odd cycles											X	

Assessments	**Screening[A]**		**Study Treatment Cycles (28 days)[B]**											**End of Treatment Visit**	**In-Study Long-Term FollowUp[V]**
Study Day	***Day -28 to -1***	***Day -8 to -1***	***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***	***Day 8***	***Day 9***	***Day 15***	***Day 21-26***	***30 Days (±2) after last study drug intake***	
12 Lead ECG [L]	X		X	X	X							[X]	X		
CBC, Serum Chemistry, coagulation, serum pregnancy test [M]		X	X C2 only									[X] C1 only	X	X	
HIV, HBV and HCV serology [N]		X													
Urine dipstick pregnancy test [O]			[X]												
Pracinostat Pop PK Sampling [P]			[X]	[X]	[X]							[X]			
Pracinostat/ placebo Administration [Q]			3 times a week/x 3 weeks												
			X		X		X			X		X			
Azacitidine Administration (Days 1-7) [R]			X	X	X	X	X	X	X						
Azacitidine Administration (Days 5-2-2) [S]			X	X	X	X	X			X	X				
Study Drug accountability/ dispensation [T]			X									[X] Compliance		X	
Adverse events/toxicity assessment [U]	X		X	X	X	X	X	X	X	X	X	[X]	X	X	
Concomitant medication review [U]	X		X	X	X	X	X	X	X	X	X	[X]	X	X	

Assessments	**Screening[A]**		**Study Treatment Cycles (28 days)[B]**											**End of Treatment Visit**	**In-Study Long-Term FollowUp[V]**
Study Day	***Day -28 to -1***	***Day -8 to -1***	***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***	***Day 8***	***Day 9***	***Day 15***	***Day 21-26***	***30 Days (±2) after last study drug intake***	
Sub-study pracinostat/AZA PK sampling (**ONLY IN SELECTED SITES**) [W]			[X]	[X]	[X]							[X]			
Biomarker Analysis [Z]	X												X even cycles	X	

Assessments noted with [X] are to be done during Cycle 1 only. All other assessments are to be done during all cycles including Cycle 1, unless otherwise specified. C = cycle.

[A] Screening Visit should occur ≤ 28 days before commencement of Cycle 1 Day 1.

[B] There is ± 4 days window allowable between each clinic visit Day 1 Cycle.

[C] Written informed consent must be obtained prior to initiation of study related procedures

[D] Inclusion/exclusion criteria must be met prior to randomization. Patients <75 years of age must have at least 1 co-morbidity, per inclusion criterion 2. Eligibility criteria, including co-morbidities, must be reviewed by Medical Monitor prior to randomization.

[E] Bone marrow aspirate/biopsy samples will be collected and evaluated for:

- **Morphologic evaluation**: at Screening (Section 6.1.1) to confirm AML diagnosis (local evaluation) and at the end of every even cycle, between Day 21 and Day 26, to evaluate the disease response to therapy at the Day 1 of each odd cycle (local evaluation). A morphologic evaluation of bone marrow already performed within 30 days prior to the ICF signature will be accepted as screening evaluation. Morphologic response assessment is required until a complete response is achieved and confirmed after 2 further cycles of treatment. At subsequent cycles, a bone marrow evaluation is no longer required, unless there is a suspicion of disease progression or relapse from CR. A bone marrow biopsy is only required in case of dry tap for the pathology interpretation of response, including bone marrow blasts.
- **Classical cytogenetics** (karyotyping), with analysis of preferably 20 metaphases (central evaluation): at screening and at each subsequent bone marrow assessment, only if screening cytogenetic is abnormal, until the patient achieves a cytogenetic complete remission.
- **MRD evaluation by MFC:** at screening and after 2 cycles from first CR
- **Biobanking for mutational analysis** (mandatory in all patients)
- If no bone marrow blood can be aspirated at screening ("dry tap", even at repeated attempts) the patient will be considered a screen failure

Peripheral blood and bone marrow fluorescence in situ hybridization (FISH) analysis for cytogenetic study and molecular analysis are not required. However if FISH testing or molecular analysis are part of the institution's standard of care, the results will be recorded in the Case Report Forms.

[F] Smoking status will be collected at screening

[G] Vital signs assessments will include: pulse rate, systolic and diastolic blood pressures (after the patient has been in the sitting or in semi-supine position for at least 5 minutes), body temperature, body weight.
Height will be only taken at screening.

Pulse rate, systolic and diastolic blood pressures will be measured:
(1) at screening
(2) pre-dose on Day 1 of Cycle 1 and Day 1 of Cycle 2
(3) at 90 minutes (±30minutes) post pracinostat/placebo administration on Day 1 of all Cycles and at Day 15 of Cycle 1
(4) at any time during the visit between Day 21 and Day 26 of Cycle 2
(5) at any time during EoT visit

Body temperature will be measured:
(1) at screening
(2) on Day 1 of all Cycles (pre-dose)
(3) on Day 15 of Cycle 1 only
(4) at any time during EoT visit

Body weight will be measured:
(1) at screening
(2) on Day 1 all Cycles
(3) at any time during EoT visit

[H] Complete physical examination will be performed at Screening.This evaluation will include an examination of general appearance, head, eyes, ears, nose, throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal and neurological.
Limited physical examination, covering general appearance, cardiovascular, lungs and abdomen body systems, will be performed at Day 1 of each cycle to assess any changes that may have occurred since the last examination.

[I] ECOG performance status will be evaluated at screening and on Day 1 of each Cycle and EoT visit

[J] Information on transfusion of RBC or platelets (including date and type of transfusion) will be collected: at Day 1 of Cycle 1 (Section 5.1.2) and between Day 21 and Day 26 of Cycle 2 and all subsequent even cycles

[K] Quality of Life Questionnaire to be administered on Day 1 Cycle 1 and on each Day 1 of odd Cycles and EoT visit

[L] Triplicate 12-lead ECGs will be recorded (after the patient has been in sitting or in semi-supine position for at least 5 minutes):
(1) at screening
(2) on Day 1 of Cycle 1(predose; at 90 minutes ±30minutes and 6 hours ±30minutes post pracinostat/placebo administration), on Day 2 of Cycle 1 (at 24 hours ±1hours post pracinostat/placebo administration), on Day 3 of Cycle 1 (at 48 hours ±1hours post pracinostat/placebo administration), on Day 15 of Cycle 1(at 90 minutes ±30minutes post pracinostat/placebo administration),
(3) on Day 1 of Cycle 2 (predose; at 90 minutes ±30minutes post pracinostat/placebo administration),
(4) during the visit from Day 21 to Day 26 of Cycle 2 (any time)
Single 12-lead ECGs will be collected 90 ±30 minutes post pracinostat/placebo administration on Day 1 of each subsequent Odd cycle (i.e., Cycles 3, 5, 7, 9, …).

[M] Laboratory tests will be performed at a central laboratory. Samples for CBC, serum chemistry and coagulation are to be collected:
(1) at screening within 8 days prior to Day1 of Cycle 1
(2) at Day 15 of Cycle 1 only
(3) at Day 1 of Cycle 2 only
(4) between Day 21 and Day 26 starting from Cycle 2 and for all the subsequent Cycles
(5) at any time during EoT visit
Hematology panel: complete blood count (CBC): hematocrit, hemoglobin, erythrocytes (RBC), platelets, leukocytes (WBC) with differential (neutrophils, lymphocytes, basophils, eosinophils, monocytes and blasts).

Blood chemistry panel: glucose, blood urea nitrogen/urea, creatinine, creatinine clearance (derived from blood creatinine value by Cockcroft formula), sodium, potassium, chloride, calcium, phosphorus, magnesium, bicarbonate/carbon dioxide (CO2), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, uric acid, albumin, and lactic acid dehydrogenase (LDH).
Coagulation panel: PT, INR, PTT, fibrinogen, D dimer
Serum beta-hCG pregnancy tests: will be performed only of women childbearing potential at the Screening visit, on Day 1 of Cycle 2, between Day 21 and Day 26 of Cycle 2 and subsequent Cycles and EoT visit.

[N] HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc and HCV serology (anti-HCV) will be evaluated centrally only at screening. HIV will be performed based on local regulation at local laboratory at screening only. HIV test already performed within 30 days prior to the ICF signature will be accepted as screening evaluation.

[O] Urine dipstick pregnancy test will be performed locally at predose on Day 1 of Cycle 1 only for women of childbearing potential.

[P] Pracinostat Population Pharmacokinetic (PK) samples will be collected on Cycle 1: 30 minutes (±15minutes), 3 hours (±30minutes) and 6 hours (±30minutes); 24 hours (±1 hour) before AZA administration; 48 hours (±2 hours) before next pracinostat/placebo dose; Day 15 any time within 24 hours after pracinostat/placebo dosing for the day.

[Q] Pracinostat/placebo will be dispensed at the beginning of each cycle. The capsules are to be taken 3 times a week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest; this scheme will be repeated every 28-day cycle. Following Cycle 1, study medication compliance will also be assessed on Day 1 of each cycle. Pracinostat/Placebo oral administration is to be taken before SC or IV injection of AZA.

[R-S] The Investigator must ensure azacitidine administration information is collected for the study, including dose changes and administration route. AZA administration: 75 mg/m^2 via SC injection or as IV infusion on the first 7 days of every 28-day cycle. If unable to accommodate the Days 1-7 schedule, then the 5-2-2 schedule may be followed. Switch between Schedule 1 and Schedule 2 during the study period is acceptable.

[T] Pracinostat/placebo will be dispensed at Day 1 of each cycle and study drug compliance will be checked. At cycle 1, compliance will be checked on Day 15 as well.

[U] AEs and concomitant medications: assessed from the signature of ICF (concomitant medications from 21 days prior to Day 1 of Cycle 1) until 30 days from last study drug administration or until initiation of new AML treatment, whichever occurs first.

[V] In-Study Long-term Follow-up: After patients permanently discontinue study treatment, they will be followed every 3 months (±1 month) from the date when study drug was last administered. Patients may be contacted during outpatient visits or by telephone. The following information will be obtained during these Follow-up contacts:

- Collect any new AML treatment
- Collect any evidence of disease progression
- Assess overall survival
- When there is a suspicion of disease progression, a bone marrow evaluation is required to confirm disease progression

[W] **(IN SELECTED SITES ONLY)** Sub-study pracinostat/AZA Pharmacokinetic (PK) samples will be collected on Cycle 1: 15 minutes (± 2 minute), 30 minutes (± 2 minute), 1 hour (± 5 minutes), 2 hours (± 5 minutes), 3 hours (± 5 minutes), 4 hours (± 5 minutes), 6 hours (± 30 minutes), 8 hours (± 30 minutes – optional sampling) after start of AZA administration; 24 hours (±1 hour) before AZA administration; 48 hours (±2 hours) before next pracinostat/placebo dose; Day 15 any time within 24 hours after pracinostat/placebo dosing for the day.

[Z] Biomarker Analysis (if consent obtained by patient): Peripheral blood samples and/or aspirate bone marrow samples will be collected and stored for potential molecular studies at screening and between day 21 and day 26 of every even cycle and at EoT visit (Section 6.4).

Schedule of Assessments - *Drug Holiday Schedule - Not recommended*

Assessments	Drug Holiday Commencement Visit	Drug Holiday Follow-up Visit [A]
Verify patient achieved a clinical remission (i.e., < 5% blasts and no circulating blasts) for a minimum of 3 cycles, and if abnormal cytogenetics at enrolment, achieved a cytogenetic CR	X	
Verify patient completed at least 12 cycles of pracinostat/placebo + azacitidine	X	
Vital signs, including weight, blood pressure, pulse rate and body temperature	X	X
Complete Physical Examination	X	
ECOG Performance Status and Quality of Life Questionnaire	X	X
Complete Blood Count (CBC) [D], Serum Chemistry		X
Bone Marrow aspirate/ biopsy & Classic cytogenetic testing		X[B]
Assess study drug compliance at prior cycle and collect all unused study drug	X	
Adverse events/toxicity assessment since last study visit	X	X
Concomitant medication review	X	X[C]

[A] Drug Holiday Follow-up visit will occur within 4 weeks (+/- 4 days) from Drug Holiday Commencement visit. A Drug Holiday for up to 1 Cycle (28 days) is allowed.

[B] If there is a suspicion of AML recurrence based on CBC results or clinical findings, a bone marrow biopsy/aspirate must be obtained to verify disease progression. In case of disease relapse from CR, patient will proceed with end of treatment visit.

[C] During the Drug Holiday Follow-up visit, confirm patient has not taken or has started another treatment regimen for AML, including another investigational product.

[D] Pregnancy test for women of childbearing potential only

Notes:

(1) Both pracinostat/placebo AND azacitidine must be discontinued while on the Drug Holiday schedule.

(2) No other AML treatment regimen, including other investigational product from another research study may be taken while on this schedule.

(3) Patients may return from their Drug Holiday schedule and resume their randomized treatment assignment at the dose that was administered prior to the Drug Holiday Commencement visit only if no relapse from CR is suspected. If there is evidence of disease progression (based on bone marrow aspirate/biopsy and/or peripheral blood) patient will proceed with End of Treatment visit.

(4) To collect overall survival information, it is important that the patient remains compliant and is responsive to the Investigator/site staff. It is strongly recommended that the patient provide back-up contact while on the Drug Holiday schedule.

Appendix B: SWOG Cytogenetic Risk Category Definitions

Risk Status	SWOG Coding
Favorable	inv(16)/t(16;16)/del(16q), t(15;17) with/without secondary aberrations; t(8;21) lacking del (9q) or lacking complex karyotypes.
Intermediate	Normal, +8, +6, -Y, del(12p)
Unfavorable	del(5q)/-5, -7/del(7q), abn 3q, 9q, 11q, 20q, 21q, 17p, t(6;9), t(9;22) and complex karyotypes (≥ 3 unrelated abnormalities)
Unknown	All other abnormalities

Slovak, 2000

Appendix C: ECOG Performance Status

Grade	Descriptions
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 housework, office work).
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities; and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken, 1982

Appendix D: Acute Myeloid Leukemia Classification - WHO 2016

CLASSIFICATION
AML with recurrent genetic abnormalities t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 APL with PML-RARA t(9;11)(p21.3;q23.3); MLLT3-KMT2A t(6;9)(p23;q34.1); DEK-NUP214 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1 AML with mutated BCR-ABL1 (provisional entity) AML with mutated NPM1 AML with biallelic mutations of CEBPA AML with mutated RUNX1 (provisional entity)
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified AML with minimal differentiation AML without maturation AML with maturation Acute myelomonocytic leukemia Acute monoblastic/monocytic leukemia Pure erythroid leukemia Acute megakaryoblastic leukemia Acute basophilic leukemia Acute panmyelosis with myelofibrosis

Arber, 2016

Appendix E: New York Heart Association (NYHA) Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256. http://trove.nla.gov.au/work/9164796?q&versionId=13288061

Appendix F: Response Criteria

Parameter	Definition
Morphologic Leukemia Free State (MLFS)	• <5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells • There should be no blasts with Auer rods • No extramedullary disease (EMD)
Morphologic Complete Remission (CR)	• <5% blasts in a bone marrow aspirate sample with spicules • There should be no blasts with Auer rods • No EMD • Absolute Neutrophil Count (ANC) ≥1,000/µL • Platelet count of ≥100,000/µL • Patient must be independent of transfusions (for at least 1 week before each assessment) *No duration of response is required for this category.* *There is no requirement to repeat a bone marrow examination if a patient normalizes their peripheral blood counts after a bone marrow sample has confirmed the presence of <5% blasts (that is, converts from MLFS or CRi to CR over time)*
Cytogenetic Complete Remission (CRc)	• Morphologic CR plus reversion to a normal karyotype (defined as no clonal abnormalities detected in a minimum of 20 mitotic cells)
Complete Remission without minimal residual disease (CR_{MRD-})	• Morphologic CR • Minimal Residual Disease (MRD) by MFC negative
Morphologic Complete Remission with incomplete blood Count Recovery (CRi)	• Morphologic CR with: - residual neutropenia (ANC<1,000/µL) or - residual thrombocytopenia (PLT<100,000/µL) • Does not require transfusion independence
Partial Remission (PR)	• Absolute neutrophil count (ANC) ≥1000/µL • Platelet count of ≥100,000/µL • A decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate* • A value of ≤5% blasts may be considered a PR if Auer rods are present * If the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%. If the pretreatment blast percentage was 20% to <49%, they must decrease by at least half to a value of ≥5%.
Stable Disease (SD)	Any designation that does not meet criteria for any CR, PR, or disease progression (PD).

Parameter	Definition
Relapse after CR	• Reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the BM not attributable to any other cause (e.g., BM regeneration after consolidated therapy)** • Appearance of new dysplastic changes • Reappearance or development of cytologically proven EMD Molecular or cytogenetic relapse: reappearance of a cytogenetic or molecular abnormality ** In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration. In such instances the date of recurrence is defined as the first date that more than 5% blasts were observed in the marrow.

Cheson, 2003

Parameter	Definition
Progressive disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/µL), and/or platelet count to >50 x 109/L (50,000/µL) non-transfused]; or • >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/µl) (in the absence of differentiation syndrome)*; or • New extramedullary disease *Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, i.e., a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate progressive disease.

Döhner, 2016

Appendix G: Examples of CYP450 1A2, 3A4 and 2C8 inducers, and CYP3A4 and CYP2C8 inhibitors of clinical relevance.

For a complete list please refer to source: FDA website - Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (Sept. 26th, 2016)

Examples of clinical inducers of CYP1A2

	Strong Inducers	Moderate Inducers	Weak Inducers
CYP1A2		Phenytoin, Rifampin, Ritonavir, Smoking, Teriflunomide	

Examples of clinical inhibitors of CYP2C8

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP2C8	clopidogrel, gemfibrozil	deferasirox, teriflunomide	telithromycin, trimethoprim

Examples of clinical inducers of CYP2C8

	Strong Inducers	Moderate Inducers	Weak Inducers
CYP2C8		rifampin	

Examples of clinical inhibitors of CYP3A4

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A4	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

Examples of clinical inducers of CYP3A4

	Strong Inducers	Moderate Inducers	Weak Inducers
CYP3A4	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, modafinil	armodafinil, rufinamide

Appendix H: Examples of CYP1A2, CYP2B6 and CYP3A4 substrates

For the complete list please refer to source: FDA website - Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (Sep 26th, 2016):

Examples of CYP1A2 substrates

	Sensitive substrates	Moderate sensitive substrates
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine	clozapine, pirfenidone, ramosetron

Examples of CYP2B6 substrates

	Sensitive substrates	Moderate sensitive substrates
CYP2B6	bupropion	efavirenz

Examples of CYP3A4 substrates

	Sensitive substrates	Moderate sensitive substrates
CYP3A4	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

Appendix I: Drugs with A Risk of Prolonging the QT Interval and/or Torsades de Pointes

Medications with a known risk of prolonging the QT interval and /or causing Torsades de Pointes are prohibited. In addition, caution should be taken when using concomitant medications with a possible or conditional risk of prolonging the QT interval and/or causing Torsades de Pointes.
The list of medications in this appendix represents an example but it is not exaustive.
The following website should be referenced as a guide for updated list of drugs which may prolong the QT interval and/or cause Torsades de Pointes:
https://www.crediblemeds.org

Drugs with a Known Risk of Prolonging the QT Interval and/or Torsades de Pointes

Amiodarone	Disopyramide	Haloperidol	Procainamide
Arsenic trioxide	Dofetilide	Ibutilide	Quinidine
Astemizole	Domperidone	Levofloxacin	Roxithromycin
Azithromycin	Dronedarone	Levomethadyl	Sevoflurane
Bepridil	Droperidol	Mesoridazine	Sotalol
Chloroquine	Erythromycin	Methadone	Sparfloxacin
Chlorpromazine	Escitalopram	Moxifloxacin	Terfenadine
Ciprofloxacin	Flecainide	Ondansetron	Thioridazine
Cisapride	Fluconazole	Pentamidine	Vandetanib
Citalopram	Gatifloxacin	Pimozide	
Clarithromycin	Grepafloxacin	Probucol	
	Halofantrine		

Drugs with a Possible Risk of Prolonging the QT Interval and/or Torsades de Pointes

Alfuzosin	Granisetron	Oxytocin	Sunitinib
Artenimol+piperaquine	Iloperidone	Paliperidone	Tacrolimus
Bedaquiline	Isradipine	Palonosetron	Tamoxifen
Clomipramine	Lapatinib	Pasireotide	Telithromycin
Clozapine	Lithium	Perflutren	Tizanidine
Desipramine	Mirtazapine	Lipid	Trimipramine
Dolasetron	Moexipril/HCTZ	Microspheres	Tramadol
Eribulin mesylate	Nicardipine	Promethazine	Tropisetron
Felbamate	Norfloxacin	Risperidone	Tolterodine
Fingolimod	Nortriptyline	Ritonavir	Vardenafil
Gemifloxacin	Ofloxacin	Saquinavir	Venlafaxine
		Sertindole	

Drugs with a Conditional Risk of Prolonging the QT Interval and/or Torsades de Pointes (Should be used with Investigator discretion)

Amantadine	Famotidine	Ketoconazole	Sertraline
Amisulpride	Fluoxetine	Lansoprazole	Solifenacin
Amitriptyline	Furosemide	Loperamide	Trazodone
Atazanavir	Galantamine	Metoclopramide	Voriconazole
Chloral Hydrate	Hydroxychloroquine	Metronidazole	Ziprasidone
Diphenhydramine	Imipramine	Olanzapine	
Doxepin	Indapamide	Paroxetine	
	Itraconazole	Quetiapine	
		Quinine Sulfate	
		Ranolazine	

Appendix J: Acceptable Contraception Methods for male and female patients of childbearing potential or female partners of male patients

I. Definition of Women of Childbearing Potential and of Fertile Men

A woman is considered of childbearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

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

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

II: Birth Control Methods Which May Be Considered as Highly Effective

These are considered methods that result in a low failure rate [<1% per year] when used consistently and correctly:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - o oral
    - o intravaginal
    - o transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - o oral
    - o injectable
    - o implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject.

Since Pracinostat may reduce the efficacy of steroid-based contraception, the use of a barrier method (male condom) is required for patients or their partners during the entire study treatment period and for 3 months after the last administration of study drug.

III. Birth Control Methods Which Are Considered Unacceptable

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhoea method
- Female condom and male condom should not be used together

Appendix K: Patient- Reported Outcomes Instrument

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Patient- Reported Outcomes Instrument (Cont.)

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent