	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

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

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.

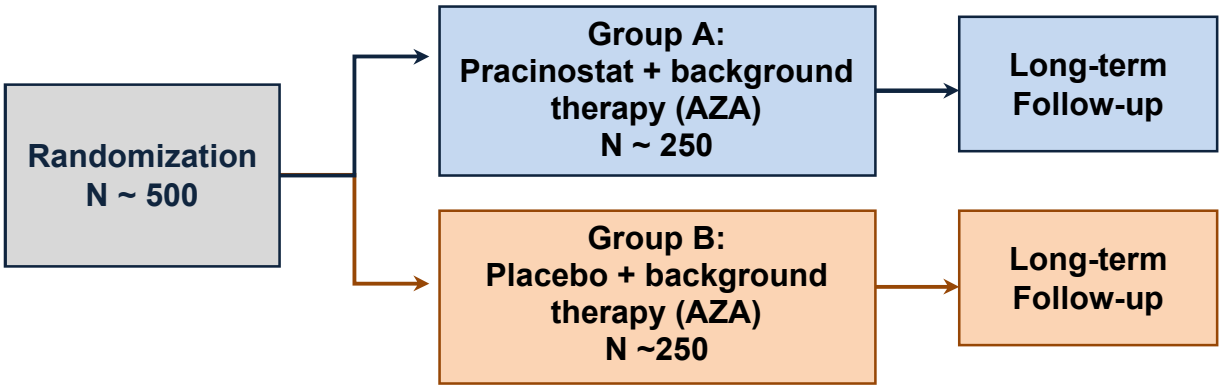
Once permanently discontinued from study treatment, patients will be followed for AEs (for 30 days) and then they will enter the Long-term Follow-up phase of the study (Section 5.2). Patients in the Long-term Follow-up phase of the study will be followed every 3 months (±1 month) for documentation of 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

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.

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**:

- 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

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.

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.

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

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.

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.

9.7.2.1 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.

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.

9.8.4 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.

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	

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

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

© Copyright 1995 EORTC Quality of Life Group. All rights reserved. Version 3.0

	[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.

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

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].

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.

- 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

- 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.

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.

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.

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).

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.

9.4 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.

9.7.3 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

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

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.

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.

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