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

Abbreviation	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
AST	Asparate Aminotransferase
ATC	Anatomical Therapeutical Chemical
AZA	AZAcitidine
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BR	Best Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
cCR	Composite Complete Remission
CI	Confidence Interval
CR	(Morphologic) Complete Remission
CRc	Cytogenetic Complete Remission
CRi	Morphologic Complete Remission with incomplete blood count recovery
CR MRD-	Complete Remission without Minimal Residual Disease
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	ElectroCardioGram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EE	Efficacy Evaluable
e.g.	For example
EORTC	European Organization for Research and Treatment of Cancer
FISH	Flourescence In Situ Hybridazation
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IDMC	Indipendent Data Monitoring Committee
INR	International Normalized Ratio
ITT	Intent To Treat
IV	IntraVenous
IWG	International Working Group
KM	Kaplan Meier
LDH	Lactate DeHydrogenase
LS	Least Squares
MedDRA	Medical Dictionary for Drug Regulatory Activities
MLFS	Morphologic Leukemia Free State
MRD	Minimal Residual Disease
NCI	National Cancer Institute
OS	Overall Survival

PD	Progressive Disease
PFS	Progression Free Survival
PH	Proportional Hazards
PK	PharmacoKinetic
PK/PD	PharmacoKinetic/Pharmacodynamic
PLT	Platelet
PP	Per Protocol
PT	(MedDRA) Preferred Term
PTT	Prothrombin Time
QoL	Quality of Life
QTc	QT interval corrected
RBC	Red Blood Cell
RFS	Relapse Free Survival
SAE	Serious Adverse Event
SAF	Safety (Analysis Set)
SAP	Statistical Analysis Plan
SC	SubCutaneous
SD	Stable Disease
SE	Standard Error
SOC	(MedDRA) System Organ Class
SWOG	South West Oncology Group
TEAE	Treatment-Emergent Adverse Event
vs.	Versus
WBC	White Blood Cell
WHO	World Health Organisation

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of safety and efficacy of pracinostat vs. placebo with azacitidine (AZA) as background therapy in patients ≥ 18 years of age with newly diagnosed acute myeloid leukemia (AML), excluding acute promyelocytic leukemia and cytogenetic low-risk AML, who are unfit to receive intensive remission induction chemotherapy due to age ≥ 75 years or comorbidities. Main efficacy objective is the comparison of the overall survival of the patients in the two treatment groups. An interim analysis for the main efficacy variable overall survival (OS) is planned after occurrence of 260 events (death due to any cause) is reported. In addition to evaluation of the pharmacokinetics of pracinostat and its metabolites managed in the main study, there will be a substudy to investigate the possible interaction of pracinosat on the pharmacokinetics of Azacitidine .
Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

2 STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective

The primary efficacy objective of the study is to show superiority in terms of overall survival (OS) of treatment with pracinostat (Group A – experimental group) versus placebo (Group B – control group) in patients treated with AZA as background therapy.

2.1.2 Secondary Objectives

Secondary objectives of this study are:

- to describe the efficacy of pracinostat by the 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

The pharmacokinetics analyses of pracinostat and the possible drug interaction of pracinostat on the PK of azacytidine will not be described in this statistical plan.

2.2 TREATMENT GROUPS

The trial has two treatment groups

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.

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.

2.3 STUDY ENDPOINTS

2.3.1 Primary Efficacy Endpoint

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

2.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- Morphologic Complete Remission (CR) rate
- Transfusion independence
- Complete Remission without Minimal Residual Disease (CR_{MRD-}) rate
- Cytogenetic Complete Remission (CRc) rate

2.3.3 Exploratory Endpoints

Exploratory endpoints are:

- Composite Complete Remission (cCR) rate
- Relapse Free Survival (RFS)
- Progression Free Survival (PFS)
- Duration of Morphologic Complete Remission (CR)
- Duration of Composite Complete Remission (cCR)
- Time to CR
- Morphologic CR within 6 cycles rate
- Quality of Life

2.3.4 PK Endpoints

PK endpoints are:

- 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

3 STUDY DESIGN

3.1 OVERALL STUDY DESIGN

This is a phase III, multicenter, double-blind, randomized study of pracinostat vs. placebo with azacitidine (AZA) as background therapy in patients ≥ 18 years of age with newly diagnosed acute myeloid leukemia (AML), excluding acute promyelocytic leukemia and cytogenetic favorable-risk AML, who are unfit to receive intensive remission induction chemotherapy due to age ≥ 75 years or comorbidities.

Patients will be randomized in a 1:1 ratio to one of two groups: Group A (experimental group) to receive pracinostat plus AZA and Group B (control group) to receive placebo plus AZA. Randomization will be stratified by cytogenetic risk category (intermediate vs. unfavorable-risk, according to SWOG Cytogenetic Risk Category Definitions, Appendix B of the protocol) and ECOG performance status (0-1 vs. 2, Appendix C of the protocol). Treatments will be administered based on 28-day cycles, with pracinostat/placebo administered orally once every other day, 3 times a week for 3 weeks, followed by one week of no treatment and AZA administered for 7 days of each cycle.
Study treatment, defined as the treatment with pracinostat/placebo (study drug) in addition to the background therapy (AZA), should continue until there is documented disease progression, relapse from complete remission (CR), or non-manageable toxicity. A minimum of 6 cycles may be required to achieve a complete remission.

Once permanently discontinued from study treatment, patients will enter the Long-term Follow-up phase (also called 'in-study long-term follow-up') of the study and will be followed for assessment of disease progression, if applicable, and survival every 3 months (±1 month) until death.

The end of this study is defined when 390 events (deaths) have occurred. Patients who are receiving study treatment at the end of the study may have the opportunity to continue to receive the study drug to which they were randomized to (Post-Study Observation Period), until the Sponsor informs the Investigators of the appropriate course of action based on the study results.
The Post-Study Observation Period is defined as the period starting from the end of the study for a maximum of 24 months.

An interim analysis at 67% (2/3) of information (260 over 390 events (deaths), being the study event-driven) will be performed for both futility (non-binding) and superiority.
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3.2 SCHEDULE OF ASSESSMENTS

Assessments	**Screening[A]**		**Study Treatment Cycles (28 days)[B]**										**End of Treatment Visit**	**In-study Long-Term Follow-Up[V]**
Study Day	***Day -28 to -1***	***Day -8 to -1***	***Day1***	***Day2***	***Day3***	***Day4***	***Day5***	***Day6***	***Day7***	***Day8***	***Day9***	***Day15***	***Day 21-26***	***30 Days (±2) after last study drug intake***	
Obtain Informed Consent[C]	X														
Randomization via IWRS			[X][D] C1 Only												
Medical history, demographics	X		[X][D] Only C1												
Bone Marrow aspirate/biopsy and classic cytogenetic testing [E]	X												X even cycles		
Smoking status [F]	X														
Vital signs [G]	X		X									[X]	X Only C2	X	
Physical examination[H]	X		X												
ECOG Performance Status [I]	X		X											X	
Transfusion of RBC or platelets [J]			X										X even Cycles		
Quality of Life Questionnaire [K]			X odd cycles											X	
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/x3 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	
Sub-study pracinostat/AZA PK sampling **(ONLY IN SELECTED SITES)**[W]			[X]	[X]	[X]							[X]			
Biomarker Analysis [Z]	X												X Even cycles	X	

SCHEDULE OF EVENTS (CONTINUED)

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.

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 of study protocol) to confirm AML diagnosis (local evaluation) and at the end of every even cycle, between Day 21 and Day 26, to evaluate the disease response to therapy at the Day 1 of each odd cycle (local evaluation). A morphologic evaluation of bone marrow already performed within 30 days prior to the ICF signature will be accepted as screening evaluation. Morphologic response assessment is required until a complete response is achieved and confirmed after 2 further cycles of treatment. At subsequent cycles, a bone marrow evaluation is no longer required, unless there is a suspicion of disease progression or relapse from CR. A bone marrow biopsy is only required in case of dry tap for the pathology interpretation of response, including bone marrow blasts.

- **Classical cytogenetics** (karyotyping), with analysis of preferably 20 metaphases (central evaluation): at screening and at each subsequent bone marrow assessment, only if screening cytogenetic is abnormal, until the patient achieves a cytogenetic complete remission.

- **MRD evaluation by MFC**: at screening and after 2 cycles from first CR

- **Biobanking for mutational analysis** (mandatory in all patients)

- If no bone marrow blood can be aspirated at screening ("dry tap", even at repeated attempts) the patient will be considered a screen failure

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

F Smoking status will be collected at screening.

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

Height will be only taken at screening.

Pulse rate, systolic and diastolic blood pressures will be measured:

(1) at screening
(2) pre-dose on Day 1 of Cycle 1 and Day 1 of Cycle 2
(3) at 90 minutes (±30minutes) post pracinostat/placebo administration on Day 1 of all Cycles and at Day 15 of Cycle 1
(4) at any time during the visit between Day 21 and Day 26 of Cycle 2
(5) at any time during EoT visit

Body temperature will be measured:

(1) at screening
(2) on Day 1 of all Cycles (pre-dose)
(3) on Day 15 of Cycle 1 only

(4) at any time during EoT visit

Body weight will be measured:

(1) at screening
(2) on Day 1 all Cycles
(3) at any time during EoT visit

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

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

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

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

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

Single 12-lead ECGs will be collected 90 ±30 minutes post pracinostat/placebo administration on Day 1 of each subsequent Odd cycle (i.e., Cycles 3, 5, 7, 9).

M Laboratory tests will be performed at a central laboratory. Samples for CBC, serum chemistry and coagulation are to be collected:
(1) at screening within 8 days prior to Day1 of Cycle 1
(2) at Day 15 of Cycle 1 only
(3) at Day 1 of Cycle 2 only
(4) between Day 21 and Day 26 starting from Cycle 2 and for all the subsequent Cycles
(5) at any time during EoT visit
Hematology panel: complete blood count (CBC): hematocrit, hemoglobin, erythrocytes (RBC), platelets, leukocytes (WBC) with differential (neutrophils, lymphocytes, basophils, eosinophils, monocytes and blasts).
Blood chemistry panel: glucose, blood urea nitrogen/urea, creatinine, creatinine clearance (derived from blood creatinine value by Cockcroft formula), sodium, potassium, chloride, calcium, phosphorus, magnesium, bicarbonate/carbon dioxide (CO2), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), totalbilirubin, total protein, uric acid, albumin, and lactic acid dehydrogenase (LDH).
Coagulation panel: PT, INR, PTT, fibrinogen, D dimer
Serum beta-hCG pregnancy tests: will be performed only of women childbearing potential at the Screening visit, on Day 1 of Cycle 2, between Day 21 and Day 26 of Cycle 2 and subsequent Cycles and EoT visit.

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

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

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

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

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

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

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

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

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

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

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

3.3 SAMPLE SIZE CONSIDERATIONS

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 alpha error spending function is from the O'Brien Fleming function for superiority and the Gamma family (with γ=-5.4695, 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 0.714286. A total of 390 events (deaths) allows to meet a power requirement of at least 90% (actually 90.87%; it was 90% with the original function used in v1 protocol; further calculations kept fixed the number of events needed) at a study-wise one-sided significance level of 0.025.

4 ANALYSIS SETS

The following set definitions will be used in study summaries and analyses: All Randomized (ITT), ITT-2, Safety (SAF), Efficacy Evaluable 1 and 2 (EE-1 and EE-2), and Per Protocol (PP), and Pharmacokinetics (PK).

Data listings will present all the collected information per patient and will be based on all screened patients in the study.

4.1 ALL RANDOMIZED (INTENTION 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 the efficacy endpoint RFS, and will be also used for the analysis of durations of response (limited to patients with response), transfusion independence and for analysis of the efficacy endpoints CR rate, CR_{MRD-} rate and for the exploratory endpoints.

Summary tables of baseline and demographic data will be calculated for the All randomized set.

A specific ITT set is also defined: 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.

4.2 SAFETY (SAF)

This set will comprise all patients who received at least one dose of 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 and some baseline characteristics.

4.3 EFFICACY EVALUABLE (EE)

4.3.1 EE-1

The Efficacy Evaluable Set will include all patients in the ITT who had a complete disease response assessment. A complete disease response assessment was 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 was 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.

4.3.2 EE-2

The Efficacy Evaluable Set will include all patients in the ITT-2 who had a complete disease response assessment. A complete disease response assessment was 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 was 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.

4.4 PER PROTOCOL (PP)

This set will comprise patients who meet all eligibility criteria and receive randomized study treatment (i.e. study drug and AZA) without major deviations or violations. This set will be the secondary set analyzed for the efficacy endpoint OS.
Membership in above defined sets, especially in the PP set, will be determined prior to unblinding.

4.5 PHARMACOKINETICS (PK)

At least two sets will be defined for the PK analysis, the first set for analyzing the pracinostat data and the other set for analyzing the azacitidine data; this last set will be limited to the patients from selected sites included in the sub-study and who consented for the sampling for the PK of azacitidine. The possibility to participate into the PK AZA sub-study will be closed as soon as the requested number of patients is reached (set at present to at least 12 for each group); due to the blindness of the study, the unblinded statistician who takes care of the analysis for the IDMC will be responsible for checking the number of patients in each group. Detailed definitions of these sets and possible additional sets will be defined in the dedicated PK SAP.

5 CONSIDERATIONS FOR DATA ANALYSIS

5.1 PROGRAMMING ENVIRONMENT

All analyses will be conducted using SAS® version 9.4 or higher.

5.2 STRATA AND COVARIATES

Patients will be randomized 1:1 to one of the two treatment groups, stratified based on the following two factors:

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

For the primary analysis the stratification used for the randomization will be used.

The results from the central assessment of the cytogenetic risk category and the ECOG grade assessed on day 1 of cycle 1 will be used as a sensitivity analysis (in case of discrepancies between the local and the central result of the baseline cytogenetic analysis leading to different cytogenetic risk categories compared to those used in the randomization process, the patient will be included in the risk category determined by the central assessment. In case the central result should not be available, the local result will be used instead).

The Kaplan-Meier estimates of the primary efficacy variable (Overall Survival) will be reported for the two treatment groups, overall and within the strata.

Also descriptive statistics (i.e. absolute and relative frequency for rates and Kaplan Meier estimates for the RFS and duration of responses) will be produced overall and within strata for the secondary and exploratory efficacy endpoints.

Other covariates with potential impact on the efficacy endpoints will be evaluated at the Blind Data Review Meeting (BDRM).

For the PK analysis demographic, physiopathological and therapeutic covariates will be used to determine the influence of these variables on PK parameters and their interindividual variability. Details will be described in the PK SAP.

Cases of randomized patients who performed a cycle with Azacitidine or Decitabine during the screening period will be evaluated at BDRM.

5.3 SUBGROUPS

The primary endpoint of OS and the secondary endpoints of CR, transfusion independence, CRc, and CR_{MRD-} will be also explored in each of the following subgroups: Intermediate Cyto risk (at randomitzation), unfavorable cyto risk (at randomization), ECOG 0-1 (at randomization), ECOG 2 (at randomization), ECOG 0-1 at Day 1 Cycle 1, ECOG 2 at Day 1 Cycle 1. In addition OS and CR will be explored in subgroups by geographical area (i.e. OS and CR analysis comparing treatments within each geographical area).
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.

5.4 MULTIPLE COMPARISONS AND MULTIPLICITY

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

The secondary efficacy outcome measures for this study are ordered as follows:

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

5.5 SIGNIFICANCE LEVEL

The overall significance level for the primary efficacy endpoint is 0.025 (one sided). As an interim analysis according to the O'Brien Fleming function for superiority and the Gamma family function (with γ=-5.4695 for non-binding futility) will be done after 260 events (2/3 of the total number of events), the respective significance levels are 0.00605 for the interim and 0.02314 for the final analysis. These significance levels will be re-computed at time of analysis based on the real fraction of information available.
Calculations of significance levels and related thresholds were performed by means of SAS PROC SEQDESIGN.

The following table shows probabilities to stop at interim analysis for futility or superiority with the null and alternative hypotheses for the primary endpoint:

Table 1 **Probability to stop at Interim Analysis** **HA as Median OS**	**10 months**	**14 months**
Gamma spending function γ=-5.4695 for futility	0.70094	0.01442
O'Brien Fleming for superiority	0.00605	0.58059

The following table shows probabilities of significant results for the first secondary endpoint, according to the chosen hierarchical procedure and assuming no need to consider the correction for multiplicity as 100% of information would be collected (which was the assumption at time of SAP V1). The reference alternative hypothesis is that the difference between treatments in the CR rate is 0.13 (having 0.20 as the rate for the placebo group). Probabilities are corrected by unconditional probability of significant results for the primary endpoint as conditional probability assumes the correlation between endpoints to be known. The obtained results are conservative and represent the lower probability bound assuming no correlation.

Table 2 **Secondary endpoint(s)** **Assumption: 100% information for secondary endpoint at interim analysis is available**		
probability of significant results	0.13 rate difference	
	Independent from primary endpoint (i.e. as it was the only endpoint in the study)	Hierarchical procedure *
at Interim Analysis	0.91	0.55
Overall	0.91	0.82

* rounded power for the primary endpoint is 0.90 overall and 0.60 at interim analysis, respectively (median OS = 14 months vs. 10 months)

However, it is now assumed that not all the patients could be recruited at time of interim look or some of them could not be followed-up for enough time and considering that correlation between the primary endpoint and the secondary endpoints cannot be assumed to be null even if difficult to quantify (no correlation would have justified not correcting for multiplicity), a procedure that manages the multiplicity due to having planned for an interim analysis is needed. The Bonferroni correction (with 0.002 and 0.023 as the partition of the overall alpha level) will be adopted, regardless of the quantity of patients and the time of follow-up. Interpretation of p-values will be based on the hierarchy defined in section 5.4. The family-wise error rate of 0.025 will be adhered to [2, 3].

According to current recruitment rate, 85% of patients on average will have been recruited before the interim analysis time.

The O'Brien Fleming bound for the primary endpoint and Bonferroni criterium for the secondary endpoint(s) will then be adopted, leading to the probability of significant results being as reported in the following table.

Table 3 **Secondary endpoint(s) - probability of significant results at Interim/Final Analysis** **Assumptions: 85% of patients randomized and Bonferroni (0.002, 0.023)**		
	0.13 rate difference	
	Independent from primary endpoint (i.e. as it was the only endpoint in the study)	Overall Hierarchical procedure **
Probability of significant results at Interim Analysis	0.56	0.34
Probability of significant results Overall	0.82*	0.74

power for the primary endpoint is rounded to 0.90 overall and 0.60 at interim analysis (median OS = 14 months vs. 10 months)
*assuming 0.6 as the probability to obtain significance at FA given failure at IA (as not all the 85% of patients will have been followed-up for more than 6 months)
** performing test on secondary endpoint also at FA in the case the primary is significant at IA but secondary is not

5.6 STATISTICAL NOTATION AND METHODOLOGY

Summary statistics for continuous variables will include the mean, standard deviation, minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Categorical

variables will be presented as frequency counts and percentages, and time-to-event variables will be summarized using Kaplan-Meier estimates including median with 95% CI, number of events, number censored.

In general, frequency tables will be presented by treatment group and overall except for efficacy analysis or otherwise specified.

Data listings will be created to support each table and to present all data.

Means, LS means, medians, and quartiles will be rounded to 1 decimal place greater than the precision of the original value, while standard deviations and SEs will be rounded to 2 decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place.

P-values will be presented with 4 decimal places and values less than 0.0001 will be presented as < 0.0001.

Unless otherwise noted, all data collected during the study will be included in data listings and will be sorted by treatment group, patient number and then by visit or event as relevant. Additional details and sorting order for each listing are presented in section 14.

In case at least one parameter in a table has missing values, a row/column with the number of missing values will be added. In case no missing values are documented at all for a table, no missing rows/columns will be presented, even if missing rows/columns are foreseen in the respective table shell.

In case more than one unscheduled visits fall in the same visit window (screening/cycle) without a value at the scheduled visit, the latest value will be included in summary tables based on cycle.

The final decision whether the PP set is relevant to the study and if tables of baseline characteristics need to be produced for the PP set, will be made at the BDRM.

5.7 DOCUMENTATION OF CLINICAL RESPONSE

Normally laboratory data needed for the assessment of clinical response are obtained from the central laboratory. In some cases, it is possible that data on peripheral blasts, neutrophil and platelet count needed for the assessment of response, are obtained from the site local laboratory when the central assessment is missing for any reason. These data will be collected in a specific form and separately listed only aimed to document response.

6 DATA HANDLING METHODS

6.1 MISSING DATA

6.1.1 Date Values

In cases of incomplete dates, the missing component(s) will be assumed as the most conservative value(s) possible.

Actual data values as they appear in the original CRFs will be shown in the data listings.

For the following dates specific imputation rules are defined:

Imputation of time to event variable dates:

Missing dates for time to event variables have to be avoided as far as possible.

The difference between the start date and the event date is calculated as time to event for the main efficacy variable and for some of the secondary variables.

Therefore the imputation of partial or complete missing event dates has to be handled using the most conservative approach. It is especially necessary to distinguish between active treatment and placebo group in this respect. As events analysed in this study are “negative” events, the following rules can be considered as conservative.

Imputation rules for missing event date

for patients who received active treatment (Pracinostat):

- If “day” is the only missing field, impute the “day” as the first day of the month documented or the last visit date within the documented month, where the absence of the event is documented.
- If “day” and “month” are missing, impute the “day” and “month” as 01 January of the year documented or the last visit date within the documented year, where the absence of the event is documented.
- If “day”, “month”, and “year” are all missing, the date of event is imputed as the date of the last visit date where the absence of the event is documented.

for patients who received Placebo:

- If “day” is the only missing field, impute the “day” as the last day of the month documented or the last visit date within the documented month, where the absence of the event is documented.
- If “day” and “month” are missing, impute the “day” and “month” as 31 December of the year documented or the last date within the documented year where the absence of the event is documented.
- If “day”, “month”, and “year” are all missing, the date of event is imputed as the date of the last visit documented where the absence of the event is documented.

For missing start dates of duration of response, rules for placebo should be used for pracinostat and viceversa, to be conservative.

Imputation of time of new AML therapies:

Missing dates for new AML therapies (either those started after study treatment stop or concomitant to study treatment stop) have to be avoided as far as possible.

The imputation of partial or complete missing start and end dates of new AML therapies have to be handled using the most conservative approach. It is especially necessary to distinguish between active treatment and placebo group in this respect. As events analysed in this study are "negative" events, the following rules can be considered as conservative.

General rules for imputation are:

- any imputed date should be before the date of death or the last day the patient was alive
- the end date of the therapy should be greater or equal to the start date of the therapy

If more than one new AML therapy is given to a patient during study period only the first start date of the new therapies is relevant for the censoring processes (selection of the first start date will be done after any imputations).

Imputation rules for missing **start date** of the first new AML therapy

for patients who received **active treatment** (Pracinostat):

- If "day" is the only missing field, impute the "day" as the first day of the month documented. If month and year are equal to the start of the study treatment impute the date as the first treatment day.
- If "day" and "month" are missing, impute the "day" and "month" as 01 January of the year documented or the start of the study treatment if the year is the same as for treatment start.
- If "day", "month", and "year" are all missing, the date of the start of the new AML therapy is imputed as the date of the start of the study treatment.

for patients who received **Placebo**:

- If "day" is the only missing field, impute the "day" as the last day of the month documented.
- If "day" and "month" are missing, impute the "day" and "month" as 31 December of the year documented or as 01 January if the year is the same as for treatment start.
- If "day", "month", and "year" are all missing, the date of event is imputed as 01 January of the year when the study treatment started.

Imputation rules for missing **end date** of the first new AML therapy

for patients who received **active treatment** (Pracinostat):

- If "day" is the only missing field, impute the "day" as the last day of the month documented.
- If "day" and "month" are missing, impute the "day" and "month" as 31 December of the year documented.
- If "day", "month", and "year" are all missing or if "ongoing" is documented, the date is imputed as the last date known alive .

for patients who received **Placebo**:

- If "day" is the only missing field, impute the "day" as the first day of the month documented.
- If "day" and "month" are missing, impute the "day" and "month" as 01 January of the year. If the year documented is equal to the year of the start of the study treatment, the date of the end of the new AML treatment is imputed as the start date of the new AML treatment.
- If "day", "month", and "year" are all missing or "ongoing" is documented, the date is imputed as the last date known alive.

Imputation of Adverse Event dates:

Missing AE dates will be queried as far as possible taking other information (eg, relatedness to study drug, first intake of study drug) into account.

For missing AE start or end date, imputation rules follow the principle that the AE is regarded as treatment-emergent AE (TEAE) when a connection to the start and end of the treatment period could not be excluded (by the documented partial dates or other relevant information in the CRF).

Imputations of adverse events are used for slotting events to the appropriate study time periods and for sorting in data listings. They will not be used to calculate duration of AEs. If an AE start or end date is missing, then the duration of the AE will be set to missing.

Remaining missing dates will be imputed as follows:

For AE start date, imputation rule is to conservatively capture AEs with missing start dates as treatment-emergent AEs (TEAEs):

- If "day" is the only missing field, impute the "day" as the first dose date if their "month" are the same. Otherwise impute the "day" as the first day of the month documented.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as the first dose date if their "year" is the same. Otherwise impute the "day" and "month" as the first of January of the year documented.
- If "day", "month", and "year" are all missing, to be conservative, the AE will be assumed to occur on the same day as the first dose was administered.

For AE end date, imputation rule is to conservatively capture AEs with missing end dates as treatment-emergent AEs (TEAEs):

- If "day" is the only missing field, impute the "day" as the last day of the month documented if their "month" are the same.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as December 31 of the year, if the patient is alive at that date. Otherwise impute the date of death.
- If "day", "month", and "year" are all missing, to be conservative, the AE will be assumed to be ongoing at the end of the study for the respective patient.

Imputation of Concomitant Medication dates

Impute start and end dates for use to derive the reference variables for concomitant medication start and end relative to treatment. The reference variables will be used to differentiate before, during and after treatment for the concomitant medication.

For concomitant medication start date, imputation rules are as follows:

- If "day" is the only missing field, impute the "day" as the first dose date if their "month" are the same and the reference variable will be set to "during treatment". Otherwise impute the "day" as the first day of the month documented.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as the first dose date if their "year" is the same and the reference variable will be set to "during treatment". Otherwise impute the "day" and "month" as the first of January of the year documented.
- If "day", "month", and "year" are all missing, do not impute completely missing concomitant medication start dates; all values that depend on this date will be set to missing. The reference variable will be set to "during treatment".

For concomitant medication end date, provided that imputed date cannot be prior to start date, imputation rules are as follows:

- If "day" is the only missing field, impute the "day" as the earliest of the last day of the month documented and the last safety assessment visit date in the documented month. The reference variable will be set to "during treatment" if the imputed date is not before first randomized study medication.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as the earliest of December 31 and the last safety assessment visit date in the documented year. The reference variable will be set to "during treatment" if the imputed date is not before first randomized study medication.
- If "day", "month", and "year" are all missing, do not impute completely missing concomitant medication end dates; all values that depend on this date will be set to missing. The reference variable will be set to "during treatment" if the imputed date is not before first randomized study medication.

6.1.2 Non-Date Values

Quality of life

Missing values will be managed according to EORTC QLQ-C30 version 3.0 manual (see reference 1 for further information).

According to this manual, scores of scales involving missing items will be computed only if at least half of the items from the scale have been answered. The scale score will be calculated by using all the items that were completed (any items with missing values will be ignored). If more than half of the items are missing (or the missing item is a single question) than the scale score will be set to missing. This will be independently applied to the calculation of each scale score (global scale score, functional scale scores, symptom scale scores)

As the analysis of the quality of life data are descriptive, no additional efforts are made to impute missing items. Especially completely missing forms will not be imputed.

Transfusion independence

In the case of missing transfusion dates no imputation will be done. However, the patient is counted as transfusion independent, if a duration of 56 days or more is calculated for two consecutive transfusions with non-missing dates. For the remaining patients with missing or incomplete transfusion dates the patient is regarded as not transfusion independent, but the final decision about transfusion independence will be taken at the BDRM, using a conservative approach.

Other non-date values

Other non-date values will not be inputed in any of the analysis.

6.2 VISIT WINDOWS

Values will be presented for all scheduled study visits according to the nominal visit obtained from the CRF. If an unscheduled visit falls in a visit window with an existing nominal visit assessment, the nominal assessment will be used for summary presentation. All unscheduled assessments are to be assigned to the latest initiated cycle based on the date of the assessment.

All visits will be included in the data listings.

6.3 STUDY PERIODS

A patient is considered to have performed a cycle if during that cycle at least one dose of either AZA or PRAN/Placebo was administered to the patient, according to the Drug administration forms (Cycle x Day 1 drug administration /Pracinostat/placebo (for PRAN/PLAC) and drug administration – azacitidine forms (for azacitidine)).

A patient is to be considered entered in the long-term follow-up if:

1. Has at least one long-term follow-up visit filled (including the visit of End of Long-term Follow-up),

OR

2. Was discontinued from active treatment phase for reasons other than death, lost to follow-up, withdrawal by subject (*).

(*) Withdrawal by subject will be considered a criterion for not entering long-term follow-up only when it is reported in the eCRF as the reason for stopping both treatment and long-term follow-up phases and the dates of stop of treatment and long-term follow-up are equal.

6.4 DATA DERIVATIONS AND DEFINITIONS

When reporting durations in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. These algorithms for durations / time to event return decimal numbers, and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

Durations and time to events will be analyzed in days.

Baseline is defined as measurement obtained at the most recent assessment prior to the date of the first study treatment dose. Change from baseline will be calculated as the difference between the respective visit value and the baseline value.

Age will be calculated from the date of birth to Screening date.

For the calculation of exposure to study drug the Body Surface Area (BSA) is needed. If the baseline BSA is not documented, the next available documented BSA within the study period will be used for the calculation of the exposure.

The following will define pre-treatment use versus concomitant medication use:

- Prior use ending before receiving the first administration of study drug will be defined as “pre-treatment medications”.
- Medications that started prior to the first administration of study drug, and continued pass through the first administered dose date as well as medication started after the first administered dose date will be defined as concomitant medications.

In a similar way, prior and concomitant procedures will be defined as:

- Prior procedures ending before receiving the first administration of study drug will be defined as “prior procedures”.

- Procedures that started prior to the first administration of study drug, and continued pass through the first administered dose date as well as procedures started after the first administered dose date will be defined as concomitant procedures.

TEAEs will be considered as any event occurring, or a pre-existing event worsening, on or after receiving the first intake of pracinostat /placebo, and up to 30 days after receiving the last administration of study drug (date reported in the field Date of Last Pracinostat/Placebo Administration in the Subject Disposition page of the CRF will be used as the reference point).
Each TEAE is collected in the eCRF by recording one initial record and one record for each change in seriousness and/or severity within the same occurrence of the event. A summary record will be derived aimed at being used for the production of the summary tables, while individual records will only be listed.

The summary record will pick-up among the collected records relevant to the same event (it is allowed to collect one field from one record and another field from another record) the maximum seriousness and the maximum severity. Actions taken will be picked up from all the records in order to keep all the actions taken with the event. The outcome will be picked up from the last record in time-sequential order. The relationship will be reconciled during data cleaning, so it will be the same in all of the records related to the same event at time of analysis.

As MRD (positive/negative) will be obtained together with the other data related to MRD analyses from the external lab, CR_{MRD-} will be derived in the CDISC datasets from CR and MRD results.

Adverse events of special interest (as described in the study protocol) will be retrieved according to the following rules reported in the table:

AESI	**MedDRA SMQ (v.20.0)**	**MedDRA PT (v. 20.0)**	**Comments**
QTc prolongation	Torsade de Pontes/QT prolongation (SMQ) - NARROW	n/a	
Supraventricular arrhythmias	Supraventricular tachyarrhythmias (SMQ) - NARROW	n/a	
Sepsis, septic shock, grade ≥3 lung infection (pneumonia), any infection leading to death	Toxic-septic shock conditions (SMQ) - NARROW	1.Any PT that includes the word sepsis 2.Exact match to the PT pneumonia or lung infection	Pneumonia only if grade ≥3

Grade ≥3 anemia, neutropenia, febrile neutropenia and thrombocytopenia	n/a	1.Any PT that includes the word anaemia. 2.Exact match to any of the following PTs: Haemoglobin decreased Band neutrophil count decreased Band neutrophil percentage decreased Febrile neutropenia Granulocyte count decreased Granulocytopenia Neutropenia Neutropenic infection Neutropenic sepsis Neutropenic colitis Neutrophil count decreased Neutrophil percentage decreased Platelet count decreased Platelet production decreased Thrombocytopenia Febrile bone marrow aplasia	All listed PTs only if grade ≥3
Grade ≥3 haemorrhage	n/a	Any PT that includes the word haemorrhage or haematoma or bleeding	All listed PTs only if grade ≥3

7 STUDY POPULATION

7.1 PATIENT DISPOSITION

Patient disposition will be presented for all screened patients. The composition of the analysis sets and strata and those who were screened, failed screening, were randomized, treated, randomized and not treated, are still ongoing, discontinued from the study treatment, entered in long-term follow-up and those who discontinued from the long-term follow-up will be summarized by treatment group and overall. Reasons for discontinuation from study treatment will be presented with frequencies and percentages for all categories: adverse event, progressive disease, death, lost to follow-up, non-compliance by subject, physician decision, pregnancy, protocol deviation, withdrawal by patient, other. Reason for discontinuation will be also reported by cycle. Number of cycles performed by patients (by category or as median number) will be reported.

Also reasons for discontinuation from long-term follow-up will be presented with frequencies and percentages for all relevant categories (lost to follow-up, death, withdrawal by patient, physician decision, study terminated by sponsor, other).

Additionaly, the number of patients where randomization code was broken by investigator together with the reason for breaking the code will be provided.

7.2 DEMOGRAPHIC CHARACTERISTICS

Demographic and baseline characteristic data will be summarized with descriptive statistics for age, gender, self-reported race/ethnicity, baseline height, baseline weight, cytogenetic risk category (central lab results and results used for randomization), and ECOG grade at baseline (used at randomization and at Cycle 1 Day 1), smoking status at baseline and descriptive statistics of numbers of cigarettes/cigars/pipes for patients who are current smokers. Additionally serology (HIV, HBV, HCV) examination at baseline will be presented. These summaries will be done for ITT, ITT-2 and SAF sets.

Baseline AML Characteristics

The following data will be summarized:

- Bone marrow blast count at diagnosis/screening (≥20% and ≤30%; and >30% categories)
- De-novo AML (defined as absence of antecedent hematological disorders and therapy-related myeloid neoplasms)
- WHO 2016 AML Classification:
  - AML with recurrent genetic abnormalities (Y/N) and types (absolute and relative frequencies)
  - AML with myelodisplasia related changes (Y/N)
  - Therapy related myeloid neoplasms (Y/N) and types (absolute and relative frequencies)
  - AML not otherwise specified (Y/N) and types (absolute and relative frequencies)
- Extramedullary disease
- Classic cytogenetic analysis results

- Cytogenetic FISH results (if done)
- Molecular analysis results (if done)
- Prior hydroxyurea for cytoreduction (Y/N obtained from the prior/concomitant medication form by considering the ATC code L01XX (hydroxyurea))
- Prior cycle with hypometylating agents (Y/N obtained from the prior/concomitant medication form by considering the ATC code L01BC (azacitidine and decitabine)).

These summaries will be done for ITT, ITT-2, and SAF sets. A listing of patients who received hydroxyurea and hypometylating agents, including details on the specific drugs, will be produced.

7.3 PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be coded with the World Health Organization (WHO) drug dictionary (B3 Enhanced format dated 01 March 2018). Version used at the start of the study will be used until the end of the study. Concomitant medications will be summarized with frequencies and percentages by drug Anatomical Therapeutic Chemical (ATC) Classification System (level 4), generic name, and treatment group. A data listing will be included that shows all medications by generic name and verbatim name. Prior anti-cancer therapies will be listed by drug (ATC level 4), generic name, and treatment group. Pre-treatment medications will be excluded from the summary table but included in the listing of all prior/concomitant medications. New anticancer therapy started during or after treatment period will be reported in a summary table (ATC level 4 and generic name), and will be listed. These summaries will be based upon the ITT set.

7.4 MEDICAL HISTORY AND PHYSICAL EXAMINATION

Medical history (non AML specific, coded with MedDRA version 20.0) will be summarized with descriptive statistics (frequencies and percentages) by medical history code and treatment group. A comprehensive data listing will also be included. These summaries will be based upon the ITT set.

AML history

Specific hematological disorders prior to study start could be entered into the CRF. The frequency and percentage of any prior hematologic disorder, the type of the hematological disorder, time from initial diagnosis of antecedent hematologic disorder to initial diagnosis of AML (months), and anti-cancer therapies will be presented in a summary table for the ITT, ITT-2, and SAF sets.

Physical examination

Baseline examinations will be presented as summary table by treatment group. The baseline examination is defined as the examination done in the screening period. Examinations performed during study follow-up will be listed. These summaries will be based upon the ITT set.

7.5 INCLUSION/EXCLUSION CRITERIA

Inclusion and exclusion criteria failures will be summarized for the screened patients by treatment group and overall in a table and also shown in a data listing.

7.6 PROTOCOL DEVIATIONS

Protocol deviations will be summarized by treatment group and category for the ITT set. Deviations will be classified as major or minor, with major deviations resulting in exclusion from the Per Protocol set. Deviations referring to assessment of the disease might have impact also on the inclusion into the EE sets. The final decision whether a protocol deviation is major or minor and the assignment to the analysis sets is made at the BDRM.

A listing of all deviations will also be included. Included in the listing will be those protocol deviations coming from the PD tracker generated during study by the CRAs and those protocol deviations coming from the specific listings generated for the BDRM by programming.

For Covid19 related protocol deviations a separate listing will be provided.

7.7 UNBLINDING OF TREATMENT INFORMATION

Patient's treatment information can be unblinded by investigator or sponsor's drug-safety department for regulatory communications. Data of patients unblinded by sponsor will be used as no impact on the conduct of the study is expected. Data obtained before the unblinding by investigator will be used in the analyses without restrictions. Overall survival data will be used without any restrictions for unblinded patients. Individual cases will be examined at the BDRM to evaluate whether a potential impact of unblinding on efficacy is to be considered.

7.8 CENSORING RULES FOR TIME TO EVENT ANALYSES

The rules for censoring of time to event variables are described in the following. Incomplete dates for the new AML therapies which are used as censoring variable in some of the analyses will be imputed using the rules described in chapter 6.1.1 of the SAP. The imputations are done prior to the use of the new AML therapies as censoring variables, so that only complete dates are used for the censoring rules.
Rules for the use of new AML therapies as censoring variable in time to event analyses:

- Treatment with HDAC is regarded as new AML therapy
- G-CSF is not regarded as new AML therapy and therefore the treatment with G-CSF is not regarded as censoring variable.
- Treatment with decitabine, Azacitidine or hydroxyurea given only for up to 3 days are not regarded as new AML therapy and therefore not regarded as censoring variables
- Treatment with Methotrexate for the treatment of Crohn's disease is not regarded as new AML therapy and therefore not regarded as censoring variable.
- A new AML therapy that started and ended before Day15 of Cycle1 of the treatment phase of the study are not regarded as censoring variable in the time to event analyses.

- If a new AML therapy started before Day15 of Cycle1 of the treatment phase of the study and ended at or after Day15 of Cycle1 then the censoring starts at Day15 of Cycle1.
- If a new AML therapy started at or after Day15 of Cycle1 of the treatment phase of the study then the new AML start date is taken as censoring timepoint.
- If more than one new AML therapies are documented for one patient then only the start of the first therapy is used as censoring timepoint.

According to protocol only hydroxycarbamide (hydroxyurea) is allowed during the first 14 days of cycle 1; the rule for this treatment was enlarged to 28 days, using a pragmatic approach.

8 EFFICACY ANALYSES

In general, efficacy analyses will be performed on the ITT set (or the ITT-2 set).

Interceding therapies are defined as new treatment for AML including salvage treatments and hematopoietic stem cell transplantation (HSCT).

8.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy endpoint is overall survival (OS) measured as the time from randomization until death from any cause. The primary set of analysis will be the ITT set.

OS time for patients alive at their last assessment of survival status will be right censored

- At the documented date of the last assessment during follow-up (which should finally correspond to the date reported in the end of long-term follow-up) in the CRF, in the case that the long-term follow-up is filled in,
- At the last assessment of survival status available in the case that the long-term follow-up is not filled in.

OS will not be censored at the time of subsequent interceding therapies, if the patient received any. Final analysis will take place after the required number of events (390 deaths) has occurred or after the decision to stop the trial because of futility or superiority at time of the interim analysis.

Missing start or end dates for the calculation of OS will be imputed as described in section 6.1.1.

The primary OS analysis will be based on the log-rank test stratified by ECOG PS and cytogenetic risk (both ECOG PS and cytogenetic risk values used for the randomization) comparing the two survival functions of the active treatment group and placebo at the overall one-sided alpha = 0.025 level of significance (a group sequential design according to Gamma family spending function, adopting γ=-3.6 (similar to O'Brien Fleming) for superiority and γ=-5.5 (more conservative than O'Brien Fleming) for futility (non-binding)) is used).

Additionally, the duration of the follow-up will be calculated using a reverse KM analysis, considering an event in patients who are alive and censoring patients at their date of death.

8.1.1 Interim Analysis

The efficacy analyses done for the interim analysis by the unblinded statistician at the CRO will be provided to the IDMC, which will provide a recommendation to Sponsor whether the study should proceed or stop due to efficacy or futility (non-binding). The efficacy criterion, which will be the basis for the IDMC recommendation together with the overall risk-benefit assessment is that the p-value of the stratified log-rank test is below the computed significance level of the interim analysis (p-value <0.00605). For the futility the significance level of 0.29906 is computed as the bound. In terms of HR, the following values are calculated: 0.73254 for the efficacy and 0.93671 for the futility evaluation, respectively. Significance levels and their counterpart in terms of HR will be re-computed at time of analysis based on the real fraction of information available. Conditional power of getting a significant result at the final analysis taking into account the results of the interim analysis will also be computed. In case of stopping of the study at the interim stage, correction to the estimation (median estimate and related CI) will be applied to reduce potential bias. Adequate SAS code will be used to produce the stratified log-rank test (PROC LIFETEST), save the test results and pass these results to the PROC SEQTEST together with the needed data from the PROC SEQDESIGN. Elaboration of data from PROC LIFETEST could be needed considering that the alternative hypothesis is one-sided.

Boundaries at time of the Interim Analysis (IA) will be recomputed having as fraction of information the number of events at IA in the ITT set / overall number of planned events (390). For calculations, the power of the test will be changed as needed to maintain the initial total number of events (390).

The proportionality of hazards will be exploratively evaluated plotting the log negative log survival distribution function for each of the treatment groups in each stratum against the log of survival days.

Selected secondary endpoints could be analyzed to provide additional information to the IDMC, if requested .

8.1.2 Final Analysis

The efficacy criterion, is that the p-value of the stratified log-rank test is below the computed significance level of the final analysis (p-value <0.02314). In terms of HR, the following value is calculated: 0.81723. Significance levels and their counterpart in terms of HR will be re-computed at time of analysis based on the real fraction of information available.

At the final stage the following analyses will be done (if the study is stopped at the interim analysis, all procedures/tests described below, as well as those related to the secondary endpoints, will be performed but considered only as exploratory; PROC SEQTEST will not be performed):

Stratified log-rank test. The proportionality of hazards will be exploratively evaluated plotting the log negative log survival distribution function for each of the treatment groups in each stratum against the log of survival days.

Appropriate methods of estimation will be applied to take into account for the sequential design. PROC SEQTEST will be adopted with the input of relevant data from PROC LIFETEST and PROC SEQTEST run at IA.

The following analysis will also be performed:

- Stratified log-rank test maintaining patients in the cytogenetic risk category assessed by the central laboratory and the ECOG PS grade as documented at Day 1 as sensitivity analysis.
- Unstratified log-rank test and Cox (PH) model including strata (cytogenetic risk factor and ECOG grade as randomized) as covariates in the model will be used as a sensitivity analysis to support evidence of efficacy. Ties will be handled using the "Efron method" in SAS. Interaction terms of the strata with the treatment groups will not be included in the model.

  The proportional hazards assumption will be exploratively evaluated by including the time dependent covariate Time x Treatment and by plotting for each covariate in the model the standardized score process of the actual data against simulated patterns based on the PH assumption (option ASSESS of SAS PROC PHREG)
- Kaplan-Meier estimates of OS in each treatment group will be reported, both overall and within strata of patients. Estimates of median survival will be provided with two-sided 95% confidence intervals, along with the first and third quartile (Q1 and Q3).
- Estimation of the hazard ratio of the two treatments by means of the Cox PH model including stratification factors and treatment.
- The number of surviving patients, the number of deaths and the number of patients with censored values will be displayed as well.
- Censoring patterns will be examined between treatment groups. Therefore the censored and not censored observations in the two treatment groups will be analyzed over time in a scatterplot.
- The effect of subsequent therapy on OS will be analyzed, including an analysis that compares OS in the treatment groups with censoring at the start date of the new interceding therapy, including those started during study treatment phase (concomitant therapy) and after stopping of study treatment as recorded in the new AML therapy eCRF page. Balance of such cases in the two treatment groups will be assessed to evaluate the appropriateness of this analysis method.
- Other sensitivity analyses will be performed to assess the robustness of OS results, if relevant. These will be decided prior to unblinding (e.g. at BDRM) based on real data.
- The primary OS analysis (stratified log-rank test) will be repeated for the PP set.
- Impact on OS of other baseline/demographic factors (including those considered for the subgroup analysis (section 5.3), plus possible others), will not be evaluated by means of Cox PH model(s) as initially planned due to the evident lack of the PH assumption for the treatment group factor.

8.2 SECONDARY ENDPOINT ANALYSES

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

- Morphologic Complete Remission (CR) rate

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

A group-sequential procedure will be applied as described in section 5.5.

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 of the protocol) in the absence of interceding therapies, including salvage treatments and hematopoietic stem cell transplantation (HSCT), within the study period. Interceding therapies, salvage treatments, as well as HSCT are collected in the "New AML Treatment" eCRF page and in the concomitant medication page (if started before and continued into the treatment period or started during treatment period). The proportions in the two treatment groups will be compared using the Cochran-Mantel-Haenszel test stratified for cytogenetic risk and ECOG PS (values stated at randomization).

The level of significance to be adopted is described in Section 5.5.

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.

Logistic regression models will be set up including also demographic characteristics (especially the AML history variables as described in section 7.2) and factors described in section 5.3 as covariates to explore the influence of these variables on CR rate (likelihood ratio test to compare different models and Wald test to evaluate covariates within a model).

Transfusion Independence

For the evaluation of transfusion independence (which is defined as achieving eight weeks or longer with neither red blood cell nor platelet transfusions during the study period), the following transfusions are regarded as "relevant" transfusions:

- Red Blood Cell (RBC) transfusions
- Platelet (PLT) infusions
- Whole Blood infusions

Transfusion independence rate is defined as the proportion of patients who achieve eight weeks or longer with no "relevant" transfusion during the study period.

The period of transfusion independence will be calculated for each patient as the duration (in days) from baseline (Cycle 1 Day 1) to the first "relevant" transfusion during the study period, and then between each subsequent "relevant" transfusion up to the last visit where this information was collected.

If at least one of the durations calculated is greater or equal to 56 days, the patient is regarded as transfusion independent within study period.

The proportion of patients who showed transfusion independence will be summarized by study treatment and transfusion dependence at baseline (patient received any kind of transfusion during the eight weeks prior to baseline).

In addition, the transfusion independence will be calculated separately for each of the relevant transfusions specified above. The porportion of patients who showed transfusion independence from RBC, PLT (whole blood transfusions are included in both categories for the calculations)will be also summarized by treatment.

The proportion of patients who are transfusion independent during study will be compared between the two treatment groups using the same methods as those used for the CR rate analysis including only treatment and stratification factor values documented at randomization. The analysis set will be the ITT set.

All transfusions will be listed.

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 of the protocol) within the study period. Absence of interceding therapies 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 including only treatment and stratification factors (values stated at randomization). Patients for whom no assessment with multi-color flow cytometry is available at the planned timepoints will be analyzed as not having reached CR_{MRD-}. However patients from sites for which no assessment of MRD was possible due to logistic reasons will be excluded from the ITT/EE-1 sets.

The current definition of the endpoint is applicable also to the patients assessed according to the scheduling given in previous protocol version.

The following rules will be applied.

- A CR should be reported in the Response form.
- A MRD negativity should be reported with a collection date (for blood) greater than or equal to collection date of BM used for declaring CR.
- No progression/relapse/PR/SD should be reported between the above dates of collection.

Cytogenetic Complete Remission (CRc) rate

The rate of Cytogenetic Complete Remission (CRc) is defined as the proportion of patients who achieve a reversion to normal karyotype at CR according to the IWG response criteria (Appendix F of the protocol) within the study period. Absence of interceding therapies 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 including only treatment and randomization factors. The endpoint will also be analyzed in EE-2 set.

8.3 EXPLORATORY ENDPOINT ANALYSES

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

Additonal to the exploratory endpoints a summary table will be generated for the best response reached during study course by each subject.

Quality of life is described in section 8.4.

Composite Complete Remission (cCR) rate

Composite complete remission (cCR) rate is defined as the proportion of patients who achieve either a disease response of CR, CRi (Morphologic Complete Remission with incomplete blood count recovery; see Appendix F of the protocol for further information) or MLFS (Morphologic Leukemia Free State; see Appendix F of the protocol for further information) (ie, cCR = CR + CRi + MLFS) within the study period, according to the IWG Criteria (Appendix F of the protocol). Absence of interceding therapies 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, limiting to the stratified analysis. Patients for whom no efficacy assessment is available will be analyzed as not having cCR when considering the ITT set.

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.
The analysis set will be the ITT set limited to patients who achieve a CR/CRi in absence of interceding therapies.

Censoring rules are:

- Time to relapse (progression) will be censored at the date of the last assessment of patient status that excluded relapse (progression). Current disease status field in the CRF page of long-term follow-up visits is to be considered as adequate information.
- In case of no 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, the influence of additional censoring criteria on RFS in the two treatment groups will be analyzed, namely censoring at the start date of a new cancer therapy instead of censoring at the date of the last assessment in the study.

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.
The analysis set will be the ITT set.

Censoring rules are:

- Time to relapse (progression) will be censored at the date of the last assessment of patient status that excluded relapse (progression). Current disease status field in the CRF page of long-term follow-up visits is to be considered as adequate information.
- 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, the influence of additional censoring criteria on PFS in the two treatment groups will be analyzed, namely censoring at the start date of a new cancer therapy instead of censoring at the date of the last assessment in the study.

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. Duration of CR will be analyzed using the same methods as those used for OS (Kaplan Meier estimates and stratified log-rank test).

Censoring rules will include the following:

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

The analysis set will be the ITT set limited to patients who achieve a CR in absence of interceding therapies.

Duration of Composite Complete Remission (cCR)

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.
- Time will be censored at the start of interceding therapies

The analysis set will be the ITT set limited to patients who achieve a cCR in absence of interceding therapies.

Time to Morphologic Complete Remission (CR)

Time to CR is defined as the time from the date of randomization until the date of first CR in the absence of interceding therapies.
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 start date of the interceding therapy, 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 stratified (cytogenetic risk and ECOG PS at randomization) log-rank test.

Morphologic Complete Remission (CR) within 6 cycles rate

Morphologic complete remission (CR) within the first 6 cycles rate is defined as the proportion of patients who achieve CR in the absence of interceding therapies within 6 treatment cycles (i.e. during treatment phase up to Day 1 of Cycle 7 included). 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, limited to the stratified analysis. Patients for whom no efficacy assessment is available will be analyzed as not having CR.

Best Response

A summary table including the best response obtained during study course will also be presented (number of patients and related percentage).
For each patient the response assessment will be classified as best response using the following criteria:

- Morphologic Complete Remission (CR) as highest level,
    - Cytogenetic Complete Remission (CRc)

followed by

- Morphologic complete remission with incomplete blood count recovery (CRi),
- Morphologic leukemia free state (MLFS)
- Partial Remission (PR),
- Stable disease (SD)
- Progression

and the two summary response classifications:

- Composite Complete Response (patients with at least MLFS)
- Overall Response (patients with CR or CRi or MLFS or PR)

The criteria used for the single responses will be adequately used also for the two summary classifications.

The analysis sets will be the ITT and the EE-1 set. The corresponding ITT-2 and EE-2 sets will be the basis for the analysis of CRc.

8.4 QUALITY OF LIFE

Quality of life will be evaluated using the EORTC QLQ-C30 questionnaire.
The following scores will be analyzed by treatment group presenting absolute score value and change from baseline for the different visits where the questionnaire was to be filled in:

- Global Health Status / QoL (questions 29, 30)
- Functional Scale "Physical Functioning" (questions 1 to 5)
- Functional Scale "Role Functioning" (questions 6,7)
- Symptom Scale / Item "Fatique" (questions 10, 12, 18)
- Symptom Scale / Item "Nausea and Vomiting" (questions 14, 15)
- Symptom Scale / Item "Appetite Loss" (question 13)

All other functional and symptom scale scores will be computed and listed. These are

- Functional Scale "Cognitive Functioning" (questions 20, 25)
- Functional Scale "Emotional Functioning" (questions 21 to 24)
- Functional Scale "Social Functioning" (questions 26, 27)
- Symptom Scale / Item "Pain" (questions 9, 19)
- Symptom Scale / Item "Dyspnoea" (question 8)
- Symptom Scale / Item "Insomnia" (question 11)
- Symptom Scale / Item "Constipation" (question 16)
- Symptom Scale / Item "Diarrhoea" (question 17)
- Symptom Scale / Item "Financial Difficulties" (question 28).

The analysis set will be the ITT set.

8.5 COMPLIANCE TO STUDY TREATMENT

During each cycle (defined from the day of current visit to the day before the next visit), a patient will be considered to be compliant with therapy if s/he takes at least 8 of the 9 capsules of study drug provided in the clinical study medication kit and at least 6 of the 7 AZA administrations (as a consequence, cycles with interruptions due to AEs are not included).

Compliance with therapy (number of patients compliant/non-compliant; percentage of compliant patients) will be summarized by cycle and by treatment group for pracinostat / placebo and for AZA.

Compliance over the whole study period will also be summarized.

A patient is regarded as compliant with therapy overall, if the ratio between the total number of capsules of study drug (pracinostat/placebo) taken and the total number of capsules expected for all the cycles performed (excluding drug-holiday period and interruptions due to AEs) for this patient is ≥8/9 and the ratio between the total number of administrations of AZA and the total number of administrations expected for all the cycles performed

(excluding drug-holiday period and interruptions due to AEs) for this patient is ≥6/7. Overall compliance will also be presented split by study drug and AZA.

The analysis set will be the ITT set.

All compliance data will be provided in data listings.

9 SAFETY

The SAF set will be used for all the analyses of safety data.

9.1 EXPOSURE TO STUDY TREATMENT

Exposure and drug dosing compliance will be summarized with descriptive statistics by treatment group. All exposure data will be provided in data listings. Exposure will be calculated for the overall study separately for pracinostat/placebo and AZA and analyzed by means of descriptive statistics:

- As treatment period duration: the end of the treatment period within one cycle is not documented in the CRF, the period duration for patients still on study treatment is therefore calculated as the scheduled last dose date minus the first dose date plus 1. For patients who already finished the treatment period, the duration of the whole study period is calculated as date of last treatment dose (pracinostat/placebo as documented in the subject disposition page of the CRF) minus the date of the first treatment (pracinostat/placebo) plus 1.

- As cumulative administered dose (summing up all the actual doses in mg). If computation is to be performed when information on current cycle is still not available (as the respective data are collected at start of the next cycle), the dose for the actual cycle will be estimated based on planned scheduling.

- As percent relative cumulative administered dose (cumulative administered dose (mg) / expected cumulative administered dose (mg) x 100). Expected dose will be based on the dose to be administered (i.e. 60 mg for pracinostat/placebo and 75mg/m^2 BSA for AZA) independently from any reduction or modification that occurred (however, drug holiday will not be included). The BSA used for the calculations will be the one measured at start of each cycle, according to protocol scheduling.

- As cumulative number of administrations.

- As cumulative number of cycles with treatment (either partial or complete). Description by categories might also be considered at time of BDRM.

- As absolute and relative frequency (percentage) of patients who reduced the dose (two possible reductions for AZA), of patients who had permanent discontinuation of treatment and of patients who interrupted treatment temporarily (overall and by reason of interruption) and patients who had drug-holiday.

AZA administration route will also be reported according to the following classification:
- IV infusion for entire study

- SC injection for entire study
- Switched between IV infusion and SC injection 1 time during study
- Switched route more than 1 time during study

Scheduling will also be categorized, based on actual administration dates, as follows:

- Number of patients on Azacitidine schedule 1 (consecutive 1-7 days) entire study
- Number of patients on Azacitidine schedule 2 (5-2-2) entire study
- Number of patients switching between 1-7 and 5-2-2 or viceversa during study
- Alternative schedules

In order to classify patients, first each cycle will be categorized as above described, then patients will be classified after exclusion of cycles with a number of administrations less than 7.
Data collected for the possible cases of drug-holiday will be listed.

9.2 ADVERSE EVENTS

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

Adverse events will be coded to the Preferred Term (PT) level using the Medical Dictionary for Regulatory Activities. Version used at the start of the study will be the most recent one published (current version 20.0), and will be used until the end of the study.

The NCI CTCAE grade for each adverse event will be documented by the treating physician in the eCRF.

A by-patient AE (including treatment-emergent, pre-treatment and post-treatment (if any)) data listing including verbatim term, PT, SOC, NCI CTCAE grade, and relationship to study treatment (AZA and Pracinostat/placebo) will be provided.

Deaths, SAEs, including those leading to death, and adverse events leading to discontinuation of study treatment or of special interest will be listed.

All AEs regardless of when they were reported will be listed.

9.2.1 Pre- and post-study adverse events

Pre-treatment AEs and post-treatment AEs (if any) will be listed.

Pre-treatment AEs are defined as adverse events starting before the first dose of pracinostat/placebo is given, and which did not worsen during treatment period.

Post-treatment AEs are defined as adverse events starting after the end of the observation period, which is defined as 30 days after the last dose of pracinostat/placebo, or start of a new therapy for AML, whichever occurs first.

However, to avoid missing important AEs, also AEs started within 30 days after last dose of pracinostat/placebo after start of a new therapy for AML will be considered as post-treatment events but will be flagged within the related listing.

9.2.2 Treatment emergent adverse events (TEAEs)

Treatment-emergent AEs (TEAEs) are defined as AEs with onset date/time at or after the start date/time of the first intake of pracinostat /placebo, or AEs with onset date/time prior to start date/time of the first intake of pracinostat/placebo that worsen in severity after the start date/time of the first intake of pracinostat /placebo, up to the end of the observation period. The observation period is defined as 30 days after the last dose of pracinostat/placebo or start of a new therapy for AML, whichever occurs first. TEAEs will be summarized by treatment group.

Where dates and/or times are missing or partially missing, AEs will be considered treatment emergent, unless there is clear evidence (through comparison of partial dates and/or times) to suggest that the AE started prior or after the study period.

The following tables will be produced:

- An overview summary of TEAEs by treatment group, including counts and percentages of patients as well as the number of events. The summary includes the following kinds of AEs:
  - any TEAE;
  - TEAEs by worst NCI CTCAE grade (only number of patients and %)
  - TEAEs by NCI CTCAE grade
  - TEAEs causally related to study drug / AZA / study drug or AZA (i.e either component of the study treatment);
  - TEAEs leading to permanent discontinuation of study treatment;
  - TEAEs leading to interruption of study treatment (separately for study drug and AZA)
  - TEAEs leading to dose reduction
  - SAEs;
  - SAEs causally related to study drug / AZA / study drug or AZA;
  - fatal SAEs;
  - fatal SAEs causally related to study drug / AZA / study drug or AZA
  - TEAEs of special interest
  - TEAEs of special interest related to study drug
- The number and percentage of patients reporting TEAEs will be provided by treatment group, System Organ Class (SOC), Preferred Term (PT), worst NCI CTCAE grade, and total. TEAEs will be sorted by SOC and PT in alphabetical order (SOC and PT within SOC).
- The number and percentage of patients reporting TEAEs together with the number of AEs, will be provided by treatment group, SOC, PT , and total. Similar table will be provided including only ≥3 worst NCI CTCAE grade. TEAEs will be sorted by frequency (based on column Total of all AEs) of a SOC and the PTs within a SOC.
- The number and percentage of patients reporting study drug (pracinostat / placebo) related (as classified by investigator) TEAEs will be provided as described for “all

TEAEs" in previous bullett. Missing relationship to study drug will be regarded as related. The number and percentage of patients reporting AZA related (as classified by investigator) TEAEs will be provided as described for "all TEAEs" in previous bullet. Missing relationship to AZA will be regarded as related.

- The number and percentage of patients reporting TEAEs either study drug (pracinostat / placebo) or AZA related (as classified by investigator) will be provided as described for "all TEAEs" in previous bullet. Missing relationship to at least one of the two components of treatment (study drug or AZA) will be regarded as related.
- The number and percentage of patients reporting TEAEs of special interest (AESIs) will be provided by treatment group, type of AESIs, PT, worst NCI CTCAE grade, and total. TEAEs will be sorted by type of AESI and PT in alphabetical order (AESI and PT within AESI). The same summary table will be provided including only TEAEs related to study drug (pracinostat / placebo). Missing relationship to study treatment will be regarded as related.
- The number and percentage of patients reporting TEAEs of special interest together with the number of AEs, will be provided by treatment group, type of AESIs, PT, and total. Similar table will be provided including only ≥3 worst NCI CTCAE grade. TEAEs will be sorted by frequency (based on column Total of all AEs) of a AESI and the PTs within a AESI. The same summary table will be provided including only TEAEs related to study drug. Missing relationship to study drug will be regarded as related.

9.2.3 Adverse events leading to dose modification and/or to discontinuation of study treatment

The number and percentage of patients reporting TEAEs leading to dose reductions, dose interruptions, and permanent discontinuation of study treatment will be tabulated in separate tables as described for "all TEAEs" in section 9.2.2. Tables related to dose reductions and dose interruptions will be additionally separated for pracinostat/placebo and AZA.

9.2.4 Serious adverse events

The number and percentage of patients reporting treatment-emergent SAEs and drug-related SAEs (study drug, AZA and either study drug or AZA) will be tabulated as described for "all TEAEs" in section 9.2.2.

9.2.5 Deaths

The number and percentage of deaths will be summarized by treatment and cause. All deaths will be additionally listed together with treatment group, dosing parameters, death date, primary cause of death and autopsy values.

Patients who died within 30 days, 60 day and 90 days from randomization will be additionally summarized.

The number and percentage of patients reporting treatment-emergent SAEs resulting in death will be tabulated by treatment group, System Organ Class (SOC) and Preferred Term (PT) (sorting for SOC and PT in alphabetical order).

9.2.6 Unblinding of treatment information

Patients where treatment information was unblinded by investigator will be listed together with treatment, date and time of unblinding.

9.2.7 Adverse events by treatment cycle

The same summary tables for adverse events described in sections 9.2.2, 9.2.3, 9.2.4 and 9.2.5 will be provided by cycle. Each AE will be assigned to only one cycle based on the date of onset. The categories in the overview summary table (number of TEAEs, NCI CTCAE grading, relationship, etc.) will be presented by treatment group and cycle.
For all the other summary tables the number and percentage of patients by treatment group, System Organ Class (SOC), Preferred Term (PT), worst NCI CTCAE grade, NCI CTCAE grade >=3, and total will be presented for each cycle. Sorting will be done as described in the relevant section. As the number of patients in higher cycle numbers may decrease, the analysis of these cycles may be not reasonable. During the BDRM it will be determined whether the analysis of cycles with a low number of patients will not be done or whether cycles will be pooled for the analysis.

9.3 SUBGROUP ANALYSES

For the following subgroups additional analyses will be performed:

- Age
  - <75 years of age at date of randomization
  - ≥75 years of age at date of randomization
- ECOG grade
  - 0-1 at date of randomization
  - 2 at date of randomization
- Renal impairment (Glomerular Filtration Rate (GFR)) at baseline, last value before first dose of pracinostat/placebo
  - Normal or high: ≥90 ml/mg/1.73m²
  - Mildly decreased: 60-89 ml/mg/1.73m²
  - Midly to moderately decreased: 45-59 ml/mg/1.73m²
  - Moderately to severely decreased: 30-44 ml/mg/1.73m²
  - Severely decreased: 15-29 ml/mg/1.73m²
  - Kidney failure <15 ml/mg/1.73m²

  The GFR value is calculated depending on the gender and serum creatinine values following the table below:

Gender	Serum creatinine	GFR equation
Female	≤0.7 mg/dl (≤62 mmol/l)	$144\ x\ \left(\frac{SCr}{0.7}\right)^{-0.329}\ x\ 0.993^{Age}[x\ 1.159\ if\ black]$
Female	>0.7 mg/dl (>62 mmol/l)	$144\ x\ \left(\frac{SCr}{0.7}\right)^{-1.209}\ x\ 0.993^{Age}[x\ 1.159\ if\ black]$
Male	≤0.9 mg/dl (≤80 mmol/l)	$141\ x\ \left(\frac{SCr}{0.9}\right)^{-0.411}\ x\ 0.993^{Age}[x\ 1.159\ if\ black]$
Male	>0.9 mg/dl (>80 mmol/l)	$141\ x\ \left(\frac{SCr}{0.9}\right)^{-1.209}\ x\ 0.993^{Age}[x\ 1.159\ if\ black]$

In the case of missing demographic information (gender and/or race) the most conservative choice of parameters in the above formulas will be used (i.e. in case of missing race, 1.159 multipler will not be used, while in case of missing gender, multiplier 141 will be used).

The following analyses will be done for each of the subgroups:

- Exposure to study drug and AZA
- Treatment Emergent Adverse Events (TEAEs)
  - Summary of TEAEs
  - Related TEAEs
  - TEAEs leading to permanent treatment discontinuation
  - Serious TEAEs
  - Related serious TEAEs
  - Serious TEAEs leading to death
  - Summary of deaths

9.4 CLINICAL LABORATORY EVALUATION ANALYSES

Clinical laboratory values (hematological panel, blood chemistry panel, and coagulation panel, as described in the clinical study protocol in section 6.2.4) will be analyzed.

Descriptive statistics will be provided for the clinical laboratory results for the SAF set by treatment cycle, as well as for the change from baseline (leukocytes differential counts expressed as percentage on leukocytes will only be listed). The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, change from baseline will be summarized for the maximum and minimum post-baseline values and the values at the "End of Treatment" visit (or the last value obtained under treatment).

Abnormal clinical laboratory results will be graded according to NCI CTCAE version 4.03, if applicable, as graded by the Central Lab (table reported in Section 15) and the grade will be presented in the by-patient data listing. Abnormal clinical laboratory test results of NCI CTCAE grade ≥ 3 will be listed within the main laboratory data listings.

The analysis of changes compared to baseline will be done as follows:

- A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI CTCAE grade, will be provided for all clinical laboratory parameters where NCI CTCAE grading is available.

Results of serology (HIV, HBV, HCV) examination at screening will be summarized for the ITT set and will be provided together with the baseline characteristics in the analysis.

9.5 VITAL SIGNS ANALYSES

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

A data listing will display all vital sign test results and findings.

9.6 ELECTROCARDIOGRAM ANALYSES

Descriptive statistics will be provided for the central ECG measurements for the SAF set by scheduled measurement times, 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. Based on NCI-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, by treatment cycle and over all post treatment evaluations (worst value) will be summarized and described in relation to baseline values.

Along with QTcF interval also JTcF interval will be assessed and will be reported by scheduled measurements times, as well as for the change from baseline. JTcF takes into account the physiologic shortening of the JT interval which occurs as the heart rate increases, permitting comparison of the JT interval across a range of rates. It is mathematically defined as:

$$JTcF\ (\text{msec}) = \frac{\text{JT}}{\text{RR}^{\frac{1}{3}}}\ (\text{msec}),$$

where JT is defined as JT (msec) = QT - QRS (msec). JTcF will be derived from ECG parametes following the formula above.

A data listing will display all ECG results and findings.

9.7 PHYSICAL EXAMINATIONS

A data listing will display all physical examination results.

10 PHARMACOKINETIC ANALYSIS

The sparse concentration-time data collected for pracinostat and its metabolite 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 metabolite(s), 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.

Details on the PK/PD methods and analysis and of the PK set(s) are provided in a dedicated SAP.

11 CHANGES TO THE PLANNED ANALYSES IN THE PROTOCOL

Version 2 of SAP was based on protocol version 3. The version 3 of the SAP reflects changes due to study protocol version 5. Version 4 of the SAP reflects minor changes needed to be implemented after the first dry-run of the data (before the Interim Analysis) and tuning of the rules for the new AML therapy. Version 5 of the SAP reflects changes decided before and during the BDRM for Final Analysis (after unblinding of the results of the Interim Analysis).

Due to FDA request the following changes were applied in the SAP, which are not reflected in the study protocol:

1) Change of the function for performing the superiority test according to a group sequential design for the primary endpoint as requested by FDA
2) Change of the parameter of the function for performing the futility test according to a group sequential design for the primary endpoint, in order to maintain the same probabilities to stop for true and wrong futility
3) Change of the method to test for secondary endpoints to overcome some possible issues reported by FDA. The new proposal by Helsinn is under further review of FDA
4) Details on the interceding therapies have been included
5) Imputation rules for interceding therapies have been included

12 REFERENCES

1. Internet page where the questionnaire and the calculations in case of missing values is described: http://groups.eortc.be/qol/eortc-qlq-c30.
2. Hierarchical testing of multiple endpoints in group-sequential trials, Ekkehard Glimm, Willi Maurer, Frank Bretz, Statistics in Medicine 2010, 29 219-228.
3. A Gatekeeping Procedure to Test a Primary and a Secondary Endpoint in a Group Sequential Design with Multiple Interim Looks, Ajit C. Tamhane, Jiangtao Gou, Christopher Jennison, Cyrus R. Mehta, Teresa Curto, Biometrics 74, 40–48, March 2018.
4. Sylvain Thepot, American Journal of Hematology, Vol. 89, No. 4, April 2014, 410-416.

13 SUMMARY OF PLANNED EFFICACY ANALYSES

At the BDRM it might be decided not to perform any analyses for the PP set (depending on the number of patients to be excluded from the ITT set) and to add analyses for sensitivity and / or additional subgroups.

Type of endpoint	Endpoint	Analysis set	Stratification	Test	Other feature	Relevance
primary	OS	ITT	ECOG, RISK (randomization)	Log-rank	none	Primary analysis for this endpoint
primary	OS	ITT	ECOG (Day 1 Cycle 1), RISK (centralized)	Log-rank	none	sensitivity
primary	OS	ITT	none	Log-rank	none	sensitivity
primary	OS	ITT	ECOG, RISK (randomization)	Cox PH	none	sensitivity
primary	OS	ITT	ECOG, RISK (randomization)	Log-rank	Censor at time of new therapy	sensitivity
primary	OS	PP	ECOG, RISK (randomization)	Log-rank	none	Secondary set
primary	OS	ITT	ECOG, RISK (randomization) + other factors	Cox PH	none	Exploratory Factors and related levels to be decided at BDRM
First secondary	CR	ITT	ECOG, RISK (randomization)	CMH	none	Primary analysis for this endpoint
First secondary	CR	EE-1	ECOG, RISK (randomization)	CMH	none	Secondary set
First secondary	CR	ITT	none	LRT	none	sensitivity
First secondary	CR	EE-1	none	LRT	none	Sensitivity on secondary set

First secondary	CR	ITT	ECOG, RISK (randomization) + other factors	Logistic regression	none	Exploratory Factors and related levels to be decided at BDRM
Second secondary	Transfusion independence	ITT	ECOG, RISK (randomization)	CMH	none	Primary analysis for this endpoint
Third secondary	CR_{MRD-}	ITT	ECOG, RISK (randomization)	CMH	none	Primary analysis for this endpoint
Third secondary	CR_{MRD-}	EE-1	ECOG, RISK (randomization)	CMH	none	Secondary set
Fourth secondary	CRc	ITT-2	ECOG, RISK (randomization)	CMH	none	Primary analysis for this endpoint
Fourth secondary	CRc	EE-2	ECOG, RISK (randomization)	CMH	none	Sensitivity on secondary set
Explorative	cCR	ITT	ECOG, RISK (randomization)	CMH	none	Primary analysis for this endpoint
Explorative	cCR	EE-1	ECOG, RISK (randomization)	CMH	none	Secondary set
Explorative	BR	ITT	none	none	none	Primary analysis for this endpoint
Explorative	BR	EE-1	none	none	none	Secondary analysis for this endpoint
Explorative	RFS	ITT	ECOG, RISK (randomization)	Log-rank	none	Primary analysis for this endpoint
Explorative	RFS	ITT	ECOG, RISK (randomization)	Log-rank	Censor at time of new therapy	sensitivity
Explorative	PFS	ITT	ECOG, RISK (randomization)	Log-rank	none	Primary analysis for this endpoint

Explorative	PFS	ITT	ECOG, RISK (randomization)	Log-rank	Censor at time of new therapy	sensitivity
Explorative	Duration of CR	ITT	ECOG, RISK (randomization)	Log-rank	Censor at time of new therapy	Primary analysis for this endpoint
Explorative	Duration of cCR	ITT	ECOG, RISK (randomization)	Log-rank	Censor at time of new therapy	Primary analysis for this endpoint
Explorative	Time to CR	ITT	ECOG, RISK (randomization)	Long-rank	none	Primary analysis for this endpoint
Explorative	CR within 6 cycles	ITT	ECOG, RISK (randomization)	CMH	none	Primary analysis for this endpoint
Subgroups	OS, CR, CRc CR_{MRD-} Transfusion independence	ITT as relevant (only the primary set)	ECOG, RISK (randomization) if feasible Otherwise unstratified	Log-rank or CMH or Logistic regression (as relevant)	Features used in the main analysis of each endpoint	Not Applicable

14 SORTING OF LISTINGS

General sorting will include strata (as randomized: cytogenetic risk Intermediate/Unfavorable, ECOG performance status 0-1/2), treatment group (Pracinostat+AZA / Placebo+AZA) and patient number.

Sorting of unscheduled visits should be managed by properly assigning to one cycle (then sorting by date).

Listings will be sorted as follows:

Listing	**Sorted by**
Listing Shell A1 Disposition of patients	GENERAL
Listing Shell A2 All protocol deviations	GENERAL
Listing Shell A3 Stratification factors	GENERAL
Listing Shell B1 Demographic characteristics	GENERAL
Listing Shell B2 Current Cancer History	GENERAL

Listing Shell B3 Prior Hematologic Disorder Antecedent to AML	GENERAL
Listing Shell B4 Left Ventricular Ejection Fraction (LVEF)	GENERAL
Listing Shell B5 Pulmunary Function Test	GENERAL
Listing Shell B6 Bone Marrow Aspirate/Biopsy	GENERAL, Cycle
Listing Shell B7 Classic Cytogenetics	GENERAL, Cycle
Listing Shell B8 Cytogenetics (FISH) (optional)	GENERAL, Cycle
Listing Shell B9 Molecular Analysis (optional)	GENERAL, Cycle
Listing Shell B10 Medical History (excluding AML specific terms)	GENERAL, SOC, PT
Listing Shell B11 Prior and Concomitant medication	prior/concomitant, GENERAL, PT, start date
Listing Shell B12 Prior and Concomitant Procedures	prior/concomitant, GENERAL, procedure, start date
Listing Shell B13 Therapy for Antecedent Hematological Disorder	GENERAL, medication, start date
Listing Shell B14 New AML treatment	GENERAL, treatment, start date
Listing Shell B15 Prior or Concomitant Medication regarded as New AML treatment	GENERAL, PT
Listing Shell E1 Overall survival	GENERAL
Listing Shell E2 Overall survival – censoring due to new interceding therapies	GENERAL
Listing Shell E3 Relapse Free Survival	GENERAL
Listing Shell E4 Relapse Free Survival – censoring due to new interceding therapies	GENERAL
Listing Shell E5 Progression Free Survival	GENERAL
Listing Shell E6 Progression Free Survival – censoring due to new interceding therapies	GENERAL
Listing Shell E7 Morphologic Complete Remission	GENERAL

Listing Shell E8 Composite Complete Remission (cCR)	GENERAL
Listing Shell E9 Cytogenic Complete Remission (CRc) only for subjects achieving CR	GENERAL
Listing Shell E10 MRD specific parameters	GENERAL, Visit, Date
Listing Shell E11 Duration of Morphologic Complete Remission	GENERAL
Listing Shell E12 Duration of Composite Complete Remission	GENERAL
Listing Shell E13 Transfusion Independence	GENERAL, Visit, Date, kind of transfusion
Listing Shell E14 Summary of efficacy results per patient and cycle	GENERAL, cycle, date of assessment, date BM/Blood
Listing Shell E15 EORTC QLQ C30	GENERAL, Visit, Type of scale, Scale, Question
Listing Shell E16 Compliance to Pracinostat/ Placebo	GENERAL, Cycle, Date dose taken
Listing Shell E17 Compliance to AZA	GENERAL, Cycle, Date dose taken
Listing Shell E18 Follow-up visits	GENERAL, Visit date
Listing Shell E19 Patients with drug holidays	GENERAL
Listing Shell F1 Exposure to Pracinostat/Placebo	GENERAL, Cycle, Week, Day
Listing Shell F2 Exposure to Azacitidine	GENERAL, Cycle, Week, Day
Listing Shell F3 Exposure to Study Drug – cumulative doses	GENERAL
Listing Shell F4 Exposure to Study Drug – cumulative number of administrations	GENERAL, Cycle
Listing Shell F5 Exposure to Study Drug – interruptions and discontinuations	GENERAL, Cycle
Listing Shell F6 Pre Treatment adverse events	GENERAL, PT, Start date
Listing Shell F7 Treatment emergent adverse events	GENERAL, PT, Start date
Listing Shell F8 Post treatment adverse events	GENERAL, PT, Start date

Listing Shell F9 Adverse events – initial and follow-up records	GENERAL, PT, Start date, Initial/Follow-up #1 to Last
Listing Shell F10 Serious Adverse Events	GENERAL, PT, Start date
Listing Shell F11 Serious Adverse Events leading to death	GENERAL, PT, Start date
Listing Shell F12 Adverse Events leading to any study treatment discontinuation	GENERAL, PT, Start date
Listing Shell F13 Adverse Events of Special Interest	GENERAL, PT, Start date
Listing Shell F14 Deaths	GENERAL
Listing Shell F15 Vital Signs	GENERAL, Visit, Parameter
Listing Shell F16 Clinical safety laboratory – hematology panel (blood counts)	GENERAL, Parameter, Visit
Listing Shell F17 Clinical safety laboratory – hematology panel (serology and HIV)	GENERAL, Parameter, Visit
Listing Shell F18 Clinical safety laboratory - chemistry panel	GENERAL, Parameter, Visit
Listing Shell F19 Clinical safety laboratory - coagulation panel	GENERAL, Parameter, Visit
Listing Shell F20 ECG results	GENERAL, Parameter, Visit
Listing Shell F21 Physical exam	GENERAL, Parameter, Visit
Listing Shell F22 Unblinding by investigator	GENERAL, Parameter, Visit

15 GRADES ASSIGNED TO LABORATORY DATA

The following table reports the grades assigned to selected laboratory parameters (according to NCI CTCAE version 4.03).

	Grade 1	Grade 2	Grade 3	Grade 4
Albumin decreased	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	missing
Alkaline Phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Alanine aminotransferase (ALT) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Activated partial thromboplastin time (APTT) prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	missing
Aspartate aminotransferase (AST) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Calcium increased	>ULN- 1.5 mmol/L	>1.5 -1.6 mmol/L	>1.6 -1.8 mmol/L	>1.8 mmol/L
Calcium decreased	<LLN - 1.0 mmol/L	<1.0 - 0.9 mmol/L	<0.9 - 0.8 mmol/L	<0.8 mmol/L
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Creatinine clearance decreased	<LLN – 60 ml/min/1.73 m2	59 – 30 ml/min/1.73 m2	29 – 15 ml/min/1.73 m2	<15 ml/min/1.73 m2
Fibrinogen decreased	<1.0 - 0.75 x LLN	<0.75 - 0.5 x LLN	<0.5 - 0.25 x LLN	<0.25 x LLN
Glucose increased	>ULN - 160 mg/dL (>ULN -8.9 mmol/L)	>160 - 250 mg/dL (>8.9 - 13.9 mmol/L)	>250 - 500 mg/dL (>13.9 - 27.8 mmol/L)	>500 mg/dL (>27.8 mmol/L)
Glucose decreased	<LLN - 55 mg/dL (<LLN -3.0 mmol/L)	<55 - 40 mg/dL (<3.0 - 2.2 mmol/L)	<40 - 30 mg/dL (<2.2 - 1.7 mmol/L)	<30 mg/dL (<1.7 mmol/L)
Hemoglobin decreased	<LLN - 10.0 g/dL (<LLN - 100 g/L)	<10.0 - 8.0 g/dL (<100 - 80g/L)	Hgb <8.0 g/dL (<80 g/L)	missing
INR increased	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	missing
Lymphocyte count decreased	<LLN - 800/mm3 (<LLN - 0.8 x 10e9 /L)	<800 - 500/mm3 (<0.8 - 0.5 x 10e9 /L)	<500 - 200/mm3 (<0.5 - 0.2 x 10e9 /L)	<200/mm3 (<0.2 x 10e9 /L)
Lymphocyte count increased	missing	>4000/mm3 - 20,000/mm3	>20,000/mm3	missing

Magnesium increased	>ULN - 3.0 mg/dL (>ULN - 1.23 mmol/L)	missing	>3.0 - 8.0 mg/dL (>1.23 - 3.30 mmol/L)	>8.0 mg/dL (>3.30 mmol/L)
Magnesium decreased	<LLN - 1.2 mg/dL (<LLN - 0.5 mmol/L)	<1.2 - 0.9 mg/dL (<0.5 - 0.4 mmol/L)	<0.9 - 0.7 mg/dL (<0.4 - 0.3 mmol/L)	<0.7 mg/dL (<0.3 mmol/L)
Neutrophil count decreased	<LLN - 1500/mm3 (<LLN - 1.5 x 10e9 /L)	<1500 - 1000/mm3 (<1.5 - 1.0 x 10e9 /L)	<1000 - 500/mm3 (<1.0 - 0.5 x 10e9 /L)	<500/mm3 (<0.5 x 10e9 /L)
Phosphorus decreased	<LLN - 2.5 mg/dL (<LLN - 0.8 mmol/L)	<2.5 - 2.0 mg/dL (<0.8 - 0.6 mmol/L)	<2.0 - 1.0 mg/dL (<0.6 - 0.3 mmol/L)	<1.0 mg/dL (<0.3 mmol/L)
Platelet count decreased	<LLN - 75,000/mm3 (<LLN - 75.0 x 10e9 /L)	<75,000 - 50,000/mm3 (<75.0-50.0 x 10e9 /L)	<50,000 - 25,000/mm3 (<50.0-25.0 x 10e9 /L)	<25,000/mm3 (<25.0 x 10e9 /L)
Potassium increased	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Potassium decreased	<LLN - 3.0 mmol/L	missing	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Sodium increased	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Sodium decreased	<LLN - 130 mmol/L	missing	<130 - 120 mmol/L	<120 mmol/L
Total bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Uric acid increased	>ULN - 10 mg/dL (0.59 mmol/L)	missing	missing	>10 mg/dL (>0.59 mmol/L)
White blood cell decreased	<LLN - 3000/mm3 (<LLN - 3.0 x 10e9 /L)	<3000 - 2000/mm3 (<3.0 - 2.0 x 10e9 /L)	<2000 - 1000/mm3 (<2.0 - 1.0 x 10e9 /L)	<1000/mm3 (<1.0 x 10e9 /L)