STATISTICAL ANALYSIS PLAN

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO COMPARE EFFICACY AND SAFETY OF ORAL AZACITIDINE PLUS BEST SUPPORTIVE CARE VERSUS BEST SUPPORTIVE CARE AS MAINTENANCE THERAPY IN SUBJECTS WITH ACUTE MYELOID LEUKEMIA IN COMPLETE REMISSION

STUDY DRUG: Oral Azacitidine (CC-486)

PROTOCOL NUMBER: CC-486-AML-001

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Prepared by:

Celgene Corporation

[redacted]

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SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) APPROVAL SIGNATURE PAGE	
SAP TITLE	Statistical Analysis Plan for A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Study to Compare Efficacy and Safety of Oral Azacitidine Plus Best Supportive Care Versus Best Supportive Care as Maintenance Therapy in Subjects with Acute Myeloid Leukemia in Complete Remission
SAP VERSION, DATE	Final, 25-JUL-2019
SAP AUTHOR	[redacted] *{See appended electronic signature page}* Printed Name and Title — Signature and Date
PROTOCOL TITLE	A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Study to Compare Efficacy and Safety of Oral Azacitidine Plus Best Supportive Care Versus Best Supportive Care as Maintenance Therapy in Subjects with Acute Myeloid Leukemia in Complete Remission
INVESTIGATIONAL PRODUCT	Oral Azacitidine (CC-486)
PROTOCOL NUMBER	CC-486-AML-001
PROTOCOL VERSION, DATE	Protocol Amendment 2.0, 08-NOV-2018
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature *{See appended electronic signature page}*

Printed Name [redacted] Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature *{See appended electronic signature page}*

Printed Name [redacted] Date _____

Lead Product Safety Physician

Signature *{See appended electronic signature page}*

Printed Name [redacted] Date _____

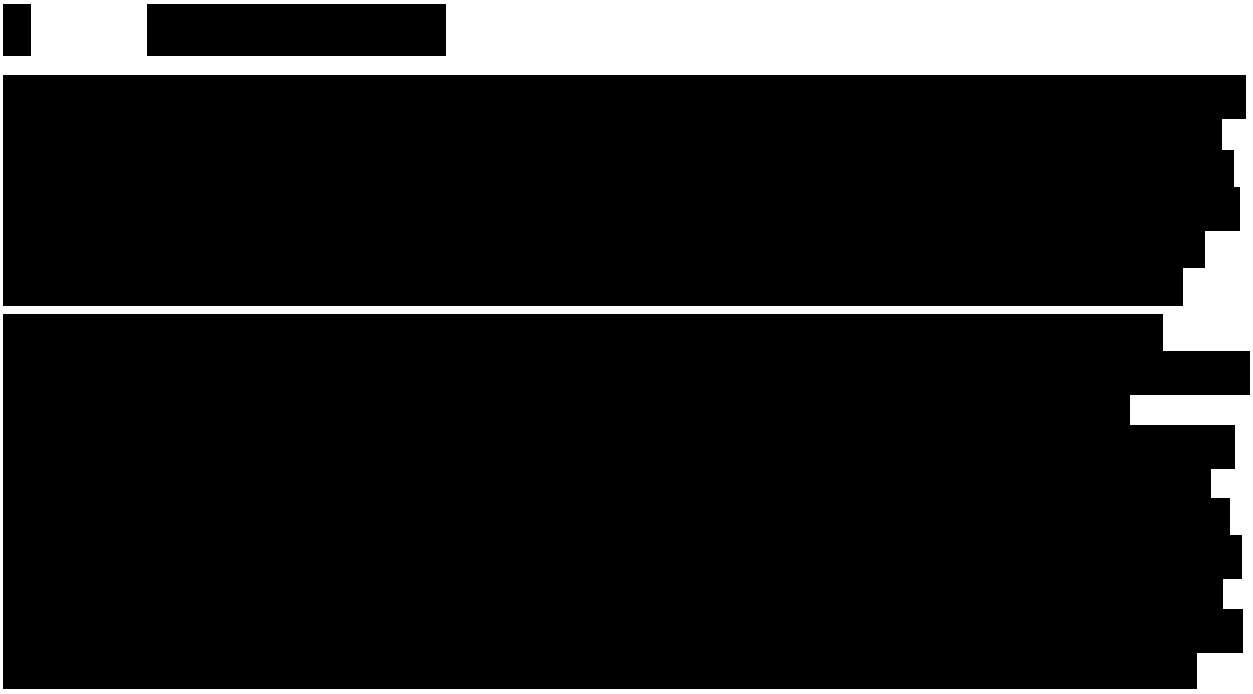
1. LIST OF ABBREVIATIONS

Table 1 Abbreviations and Specialist Terms

AE	Adverse event
ALT	Alanine transaminase (also known as SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate transaminase (also known as SGOT)
ATC	Anatomical therapeutical chemical
AZA	Azacitidine
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMML	Chronic myelomonocytic leukemia
CR	Complete remission
CRc	Complete cytogenetic remission
CRi	Complete remission with incomplete blood count recovery
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of study
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
FAB	French-American-British

FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
Hgb	Hemoglobin
HR	Hazard ratio
HRQoL	Health-related quality-of-life
IP	Investigational product
IPCW	Inverse probability of censoring weighted
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LDH	Lactic dehydrogenase
MDS	Myelodysplastic syndrome
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	Modified intent-to-treat
MRD	Measurable/Minimal Residual Disease
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NA	Not applicable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial Remission

QD	Once a day
RFS	Relapse-free survival
ROW	Rest of the world
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SDev	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase (also known as AST)
SGPT	Serum glutamic pyruvic transaminase (also known as ALT)
TEAE	Treatment-emergent adverse event
TTP	Time to progression
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization



3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the study is to demonstrate if maintenance therapy with oral azacitidine improves overall survival (OS) compared with placebo in subjects with AML, age ≥ 55 years, who have achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) after induction with intensive chemotherapy with or without consolidation chemotherapy.

3.2. Secondary Objectives

The secondary objectives of the study are:

- To determine relapse-free survival (RFS);
- To determine safety, tolerability; and
- To determine the effect of oral azacitidine compared with placebo on health-related quality-of-life (HRQoL) and healthcare resource utilization.

[redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is an international, multicenter, placebo-controlled, phase 3 study with a double-blind, randomized, parallel-group design in subjects with *de novo* AML or AML secondary to prior diagnosis of myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) aged ≥ 55 years, who are in first CR/CRi following induction therapy with or without consolidation chemotherapy.

The study consists of 4 phases; Pre-randomization Phase, Treatment Phase, Follow-up Phase, and Extension Phase.

4.1.1. Pre-randomization Phase

Newly diagnosed subjects, ≥55 years of age, who have a confirmed diagnosis of AML according to the criteria set by the World Health Organization (WHO) 2008 classification (Swerdlow, 2008), who have achieved first CR/CRi status after induction therapy with/without consolidation therapy will be eligible for randomization (within 4 months [± 7 days] of achieving first CR/CRi). Screening procedures are to occur during the Pre-randomization Phase, within 28 days prior to randomization. Subjects will provide informed consent prior to undergoing any study related procedures.

4.1.2. Double-blind Treatment Phase

Following confirmation of eligibility at screening, approximately 460 subjects will be randomized 1:1 to receive 300 mg oral azacitidine once a day (QD) or placebo, for 14 days of each 28 day cycle. Randomization will occur by a central randomization procedure using an Interactive Voice Response System (IVRS). Subjects are stratified by years of age at the time of induction therapy (55-64 versus ≥ 65), prior history of MDS (yes versus no), cytogenetic risk category (intermediate risk versus high risk), and received consolidation therapy following induction therapy (yes versus no).

After randomization, no crossover between the treatment arms will be permitted at any point during the study.

During the double-blind treatment phase, subjects will be assessed for safety, tolerability and efficacy.

4.1.3. Follow-up Phase

All treatment discontinued subjects, regardless of reason for discontinuation, should undergo end-of-study procedures at the time of treatment discontinuation visit. Subjects will have a follow-up visit for the collection of AEs up to 28 days after last dose or up to the end-of-treatment visit, whichever is longer. After this follow-up visit, subjects will be followed for survival, by telephone, every month for the first year and then every 3 months until death, withdrawal of consent for further follow-up, study end, or until a subject is lost to follow-up. Discontinued subjects will not be replaced.

4.1.4. Extension Phase (EP)

Upon a site's IRB/IEC approval of Protocol Amendment 2 which allows for an EP, after study unblinding by Celgene, any subject randomized to the oral azacitidine arm, who continues to receive oral azacitidine, who demonstrates clinical benefit as assessed by their Investigator, and consents to participate in Extension Phase, may continue to receive oral azacitidine in the EP (at their current dose) at the start of their next cycle. To receive oral azacitidine in the EP, the subject must not have been discontinued from receiving IP prior to entering this EP of the study. Subjects randomized into the placebo arm will discontinue treatment and will not receive oral azacitidine in the EP. However, upon consent, these subjects may be transitioned into the EP and followed for survival.
In addition, any subject who was discontinued from the treatment phase (irrespective of randomization arm), upon providing additional consent, may enter the EP, where they will be followed for survival (without receiving oral azacitidine) for at least another 12 months, until death, withdrawal of consent or study closure, or lost to follow-up.

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is OS, defined as time from randomization to death from any cause.

4.2.2. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is Relapse-free survival (RFS) which is defined as time from randomization to the date of documented relapse or death from any cause, whichever occurs first.

4.2.3. Additional Secondary Efficacy Endpoint(s)

The additional secondary efficacy endpoints are:

- Time to relapse;
- Time to discontinuation from treatment;
- Patient-reported outcomes utilizing the FACIT-Fatigue Scale and the EQ-5D; and
- Measures of healthcare resource utilization.

4.2.4. Safety Endpoints

The safety endpoints include:

- Type, frequency, severity, and relationship of adverse events to study treatments;
- Physical examinations;

- Vital signs;
- Clinical laboratory evaluations;
- Concomitant medication/therapy.

[redacted]

The analysis methods and timing of analysis for the quality of life endpoints are described in a separate pharmacoeconomics SAP.

[redacted]

4.3. Stratification, Randomization, and Blinding

Randomization will be carried out using an Interactive Voice Response System (IVRS). Treatment assignment will follow a 1:1 ratio between two treatment arms. Randomization method was based on permutated-block randomization. Randomization was stratified by the following factors: age at time of induction therapy (55-64 versus ≥ 65 years); prior history of MDS (yes versus no); cytogenetic risk category at time of induction therapy (intermediate risk versus poor risk); received consolidation therapy following induction therapy (yes versus no).

This is a double-blind study. Subjects, investigators, site staff and Celgene Corporation clinical and medical personnel will be blinded of treatment assignments until database lock.

4.4. Sample Size Determination

The equality of OS curves will be compared between the oral azacitidine and placebo treatment arms using a stratified log-rank test. Assuming a median OS of 16 months in the placebo treated group ([redacted]), a median OS of 22.9 months in the oral azacitidine treated group (43% improvement), and a study duration of 60 months with a drop-out rate of 5% from both treatment arms, over the duration of the study, this design requires 330 deaths and approximately 460 subjects (230 per treatment arm) to be randomized in order to achieve at least 90% power to detect a constant hazard ratio of 0.70 and demonstrate a statistically significant difference in OS. It is assumed that the OS distribution is exponential with a constant failure (hazard) rate and that accrual is non-uniform during an accrual period of 36 months with 25% of the subjects accrued during each of the first 2 years of enrollment (50% accrued at 24 months) and the remaining 50%

accrued during the last year of enrollment. Sample size calculations are based on a one-sided alpha of 0.025 with one interim analysis for futility after 30% of the events have occurred.

Sample size was calculated using the East® Version 5.4 software system [redacted]).

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the following:

Program source (e.g., SAS program name, including the path that generates the output), source data (e.g. derived dataset, raw datasets, etc) and data extraction date (e.g., the database lock date, run date.)

The purpose of the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference. An output date will also appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting the corresponding tables and/or figures.

Summary statistics for continuous variables include sample size (n), mean, standard deviation (SDev), median, minimum, the 25th (Q1), and 75th (Q3) percentiles, and maximum. All mean and median values will be formatted to one more decimal place than the measured value. SDev values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value. Frequency summary for categorical variables includes number and percentage. All percentages will be rounded to one decimal place. Number and percentage values will be presented as xx (xx.x%). All analysis and summary tables will have the population sample size for each treatment arm in the column heading. All p-values (2-sided) will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999'. Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently in specific analysis. All laboratory data will be reported using standard international (SI) units, unless specified otherwise.

All listings will be sorted for presentation in order of treatment arm, study center, subject, and date of procedure or event.

The day of the first dose of any study drug will be defined as Study Day 1.

Baseline value is defined as the last non-missing value on or before randomization date, unless specified otherwise. If multiple values are present for the same date, the average of these values will be used as the baseline, unless specified otherwise.

5.2. Analysis Populations

5.2.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population includes all subjects who are randomized, regardless of whether they received study treatment or not. Subjects will be analyzed based on randomized treatment arm. The ITT population will be used for the analysis of the primary and secondary efficacy endpoints.

5.2.2. Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population includes all subjects who have met inclusion/exclusion criteria and experienced no protocol violations (as defined below) and have received a minimum of 1 cycle of treatment. Subjects will be analyzed based on randomized treatment arm.

Protocol violations leading to exclusion from the mITT population are defined as any of the following:

- No presence of CR/CRi at baseline as programmatically determined by central laboratory data
- Had at least one inclusion or exclusion criteria violation;

5.2.3. Safety Population

The safety population includes all randomized subjects who have received at least 1 dose of study drug.

Drug exposure and all safety analyses will be based on the safety population, unless specified otherwise.

6. SUBJECT DISPOSITION

All subjects screened/randomized will be included in these analyses.
The disposition of subjects will be summarized with counts and percentages. Summaries will include the number of subjects screened and randomized.

For subjects randomized, subject disposition will be summarized for analysis population by treatment arm and overall for:

- ITT Population
- mITT Population
- Safety Population

A listing of reasons for exclusion from the mITT Population will be provided. A separate listing will be provided for subjects not randomized (screen failures) with reasons for screening failure. Listings will be provided for subjects randomized but not treated, and for discontinued subjects with reason for treatment discontinuation.

Reasons for discontinuation from the study treatment phase will be collected on the CRF and will be summarized for all randomized subjects with the following

- Disease relapse
- Adverse event
- Subject withdrew consent
- Physician decision (become eligible for allogeneic bone marrow or stem cell transplantation during treatment period)
- Death
- Subject lost to follow-up
- Protocol violation
- Other

Reasons for discontinuation from the study will be collected on the CRF and will be summarized for all randomized subjects with following:

- Death
- Adverse event
- Pregnancy
- Progressive disease
- Lack of efficacy
- Recovery
- Withdrew consent
- Non-compliance with study drug
- Lost to follow-up
- Study terminated by sponsor
- Transition to commercially available treatment
- Protocol violation
- Other

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and reported by site and assessed by clinical research physician or designee following company standard operational procedure. The protocol violations will be summarized by treatment arm for the ITT population.

A by-subject listing of subjects with protocol deviation in the ITT population will be provided. A by-subject listing of subjects with protocol violations in the ITT population will also be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics, baseline characteristics, medical history, prior therapy, and prior medications will be presented for the ITT and safety populations. Data summaries will be presented by treatment and overall. Individual subject listings will be provided to support the tables.

8.1. Demographics

Demographic characteristics consist of age, sex, race, ethnicity, geographic region, weight (kg), height (cm), and body mass index (BMI).

Age, height, weight and BMI will be summarized using descriptive statistics. Sex, race, ethnicity, geographic region, and age categories will be summarized with counts and percentages.

Age is calculated as described in section 17.1.2.

8.2. Baseline Characteristics

Baseline clinical characteristics, including the initial WHO AML classification, type of AML (primary or secondary), cytogenetic risk status at time of induction therapy, MRD status at randomization, prior history of MDS/CMML and type (primary or secondary), Eastern Cooperative Oncology Group (ECOG) Performance Status at randomization, CR/CRi status after induction therapy, CR/CRi status at randomization, consolidation therapy received or not, cycles of conlidation therapy received and reasons of not eligible for transplantation will be summarized using frequency distributions (count and percent).

Baseline clinical characteristics, including percentage of bone marrow blasts (%), peripheral blood blasts (%), Hgb (g/dL), platelet count (x 10^9/L), ANC (x 10^9/L) and WBC (x 10^9/L) will be summarized using descriptive statistics. In general, the baseline value is the last non-missing assessment on or prior to the date of randomization, unless otherwise specified.

The following time intervals will be summarized using descriptive statistics:

- time (months) from initial AML diagnosis to randomization;
- time (months) from start of induction therapy to randomization;
- time (days) from start of induction therapy to first achieving CR/CRi;
- time (days) from first achieving CR/CRi to randomization

Results of the baseline chest x-ray, ECG, pregnancy status will be provided in by-subject listings.

8.3. Medical History

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Affairs (MedDRA) Version 22 using frequency distributions (counts and percentages).

Individual subject listings will be provided to support the table.

8.4. Prior Therapy

8.4.1. Prior Induction Therapies and Consolidation Therapies for AML

All prior induction therapies for AML will be summarized in frequency tabulations (subject counts and percentages). The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization (WHO) (March 2019 version) will be used to group prior induction therapies for AML into relevant categories for these tabulations.

Similar summary table will be provided for consolidation therapies for AML.

Individual subject listings will be provided to support the summary tables.

8.4.2. Prior Cancer History and Related Procedures/Surgeries, Radiation and Regimen Therapies

By-subject listing of prior cancer history, type of therapy received, diagnostic exams for cancer prior to screening for the study and related prior procedures/surgeries, prior radiation treatment and prior regimen treatments for cancers not under study will be provided.

8.5. Prior Medications

Prior medications are defined as medications that were started on or prior to the date of randomization. Prior medications that continue past the date of randomization will also be reported as concomitant medications. The ATC coding scheme of the WHO (March 2019 version) will be used to group medications into relevant categories for these tabulations.

Individual subject listings will be provided to support the tables.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

All analyses of treatment exposure will be conducted using the safety population, unless otherwise specified.

Descriptive statistics of treatment duration, cumulative dose, dose intensity and average daily dose will be presented by treatment arm. Individual subject listings of drug exposure as recorded in CRF will be provided to support the tables.

9.1. Treatment Duration

Treatment duration and number of days dosed will be summarized by treatment arm.

Treatment duration is defined as treatment end date – first dose date +1, where treatment end date is last dose date + 14 days (the prescribed rest period of each cycle), or the death date, whichever is earlier.

Total Person-years of treatment duration will be calculated as the sum of treatment duration (days)/365.25 across all subjects.

Total number of days dosed is defined as the total number of days the subject took a non-zero dose of study drug.

See Section 17.1.3 for cycle length and cycle number calculations. Average cycle length (days), average number of days dosed per cycle, and number of treatment cycles will be summarized by treatment arm. The number of days dosed per cycle is defined as the number of days the subject received a non-zero dose within that cycle. Average cycle length for a subject is defined as treatment duration in days divided by the number of cycles. Number of days dosed per cycle is defined as the total number of days dosed during the entire treatment period /number of cycles. For average cycle length and average number of days dosed per cycle, a single average value will be computed for each subject and then the descriptive statistics will be computed for each treatment arm. Additionally, the count and percent of subjects by number of cycles of treatment will be provided for each treatment arm.

9.2. Cumulative Dose and Dose Intensity

Cumulative dose is defined as the sum of all doses taken across the entire treatment period (in mg). Average daily dose (mg/day) is defined as the cumulative dose divided by the total number of days dosed.

Actual dose intensity during the treatment is defined as the cumulative dose divided by the treatment duration, which is defined as in Section 9.1.

Relative dose intensity (RDI) is defined as the ratio of actual dose intensity to the planned dose intensity, which is 300mg/day × 14 days/28days=150mg/day for all subjects.

The overall relative dose intensity will be categorized into < 75%, 75% to 85%, 85% to 100%, and > 100%, and frequency counts will be provided by treatment arm.

In addition, treatment exposure as described in section 9.1 and 9.2 will also be analyzed for subjects with dose escalation, which is defined as subjects who have at least one assigned dose

regimen of 300mg × 21/28 days. In these analyses, the first dose date refers to the first dose date of the treatment period where the assigned dose regimen is 300mg × 21/28 days.

9.3. Dose Adjustments

Dose adjustments (including dose escalation and dose reduction), as reported in the dose exposure CRF page, will be summarized by treatment arm and include the following:

- Any dose adjustments;
- Dose adjustment due to AE;
- Dose adjustment due to AML relapse/progression;
- One dose reduction;
- Two dose reductions;
- Dose escalation (to 300mg × 21 days).

Dose adjustment is defined as subjects who have reported at least one dose adjustment in the dosing CRF page. One dose reduction is defined as subjects have reduced assigned dose from 300mg × 14 days to 200mg × 14 days. Two dose reduction is defined as subjects have reduced assigned dose from 300mg × 14 days to 200mg × 14 days, and then from 200mg × 14 days to 200mg × 7 days. Dose escalation is defined as subjects who have received at least one assigned dose of 300mg × 21 days.

In addition, time to first dose adjustment due to AE, time to first dose adjustment due to AML relapse/progression, reason for first dose adjustment and reason for first dose escalation will also be summarized.

9.4. Treatment Compliance

As part of the routine recording of the amount of IP taken by each subject, the dose start and end dates, dose assigned and actual dose administered will be recorded in the CRF. These records will be used to calculate compliance.

The compliance rate (%) for each subject will be computed as 100 times the cumulative dose (in mg) taken over the period divided by the intended cumulative dose (in mg) that should have been taken over the same period. It will be calculated for each subject for each cycle of treatment and overall.

Overall compliance will be summarized using descriptive statistics overall and by cycle. Additionally, the number and percentage of subjects will be summarized by category < 75%, ≥75 to ≤ 120%, and > 120%.

11. EFFICACY ANALYSIS

All efficacy evaluations will be conducted using the ITT population. Supportive analysis of the primary and key secondary efficacy endpoints using the mITT population will be conducted. Statistical comparisons will be made between oral azacitidine and placebo.

11.1. General Statistical Methods

All hypothesis testing will be carried out at the 5% (2-sided) significance level and designed to evaluate the superiority of oral azacitidine relative to Placebo.

The study randomization scheme was stratified according to 4 prognostic features: age at time of induction therapy 55-64 versus ≥ 65 years; prior history of MDS: yes versus no; cytogenetic risk status at time of induction therapy: intermediate risk versus poor risk; and received consolidation therapy following induction therapy: yes versus no, resulting in 16 strata. The statistical analyses conducted to compare treatment arms will include methods that are stratified according to the randomization scheme, using the stratification factors as collected in the clinical database (for subject with missing stratification factor, the missing stratification factor value will be imputed by the data entered via the IVRS). Additionally, for primary endpoint OS and key secondary endpoint RFS, the stratified analysis using IVRS data may also be conducted. It is possible that the number of subjects in an individual stratum may be very small. In order to facilitate inferential statistical analysis, if the minimum number of subjects in a stratum is less than 16 (irrespective of treatment arm), then only the 3 stratification variables that result in the largest minimum stratum size will be used for analysis purposes. Analyses will not be stratified by investigative center, as the recruitment for many centers is likely to be very small.

The general procedure for the analysis of the time-to-event efficacy variables will be as follows. Time-to-event variables will be measured in days but presented in months on tables and figures. A Kaplan-Meier (KM) survival analysis will be performed (unadjusted for the stratification variables). The resulting survival estimates will be presented graphically for selected endpoints. The median, 25th and 75th percentile time-to-event data will be presented with 95% confidence intervals (CIs) (if they can be estimated). The numerical difference (and CI of the difference) in the median, 25th and 75th percentiles between oral azacitidine and placebo will be presented for the unstratified analysis. Differences will be calculated as oral azacitidine - placebo. The 95% CI for the difference will be derived using Kosorok's method ([redacted]). One-year and two-year survival rates with 95% CIs and the difference in survival rates between oral azacitidine and placebo with 95% CI for the difference will also be presented for OS. The CI for the difference between treatment arms in the 1-year proportions will be calculated using Greenwood's variance estimate [redacted]).

For the primary efficacy analysis of OS, oral azacitidine will be compared to placebo using the stratified log-rank test to assess superiority. The null hypothesis is that the survival curves are equivalent. The stratified Cox proportional hazard regression model will be used to estimate the hazard ratio (HR) and associated 95% CIs for the HR.

The censoring distributions of the treatment arms will be assessed using KM methods. Reverse KM estimates for OS will be calculated to assess the censoring distributions, where observations

in the original analysis that were events (i.e., deaths) will be censored and observations that were censored will be treated as events. The median, 25th and 75th percentiles will be presented and KM curves will be displayed graphically by treatment arm. Additionally, reasons for censoring (e.g., lost to follow-up, withdrew consent, alive at data cut-off) will be summarized (n, percent) for the OS endpoint. The median of the reverse OS KM distribution will be used as the estimate of the median follow-up time [redacted]

In order to accommodate tied time-to-event data, the EXACT option within SAS PROC PHREG will be used. This method assumes that there is a true but unknown ordering for the tied event times, and that the ties are merely the results of imprecise measurements of time.

For the categorical efficacy variables, comparison of treatment arms will be via Fisher's exact test, ignoring strata.

A sequential gate-keeping approach will be used to control the overall type I error rate in order to perform hypothesis testing on multiple endpoints. Two endpoints, the primary efficacy endpoint of OS and the key secondary endpoint of RFS, will be tested sequentially in the pre-specified order. The primary efficacy endpoint will be tested first at the two-sided 0.05 significant level. In order to preserve the overall alpha level at 0.05 across the OS and RFS endpoints, formal statistical inference for the RFS analyses can only be made if superiority of oral azacitidine is demonstrated for the primary efficacy endpoint OS, at the two-sided 0.05 significance level.

Other than the pre-specified sequential testing of OS and RFS, no additional alpha adjustments for multiplicity will be made.

11.2. Analysis of Primary Efficacy Endpoint

The primary efficacy variable, time from randomization to death from any cause will be defined as the number of days from the date of randomization until the date of death from any cause, and is calculated by the formula: date of death - date of randomization + 1. Subjects surviving at the end of the follow-up period, or who withdraw consent, or who are lost to follow up will be censored at the date last known alive. For subjects who have withdrawn consent during the study, the last date known alive will be the date of consent withdrawal from the study. For all other subjects, the last date known alive will be derived by searching through all valid assessment dates in all study datasets to identify the last valid subject assessment date available for each subject.

11.2.1. Primary Efficacy Analysis

The primary efficacy analysis will be performed using the ITT population. The null hypothesis for testing the primary efficacy endpoint, time to death from any cause, is that the overall survival distributions for the oral azacitidine and placebo groups are equivalent. The analysis of the primary efficacy endpoint will be conducted using a stratified log-rank test, stratifying by age at time of induction therapy, prior history of MDS, cytogenetic risk category, received consolidation therapy following induction therapy. The p-value from the stratified log-rank test will be the p-value for primary analysis. The p-value from unstratified log-rank test will also be

provided. The KM method will be used to estimate the survival distribution functions for each treatment arm. KM estimates for median OS as well as the 25th and 75th percentiles and associated two-sided 95% CIs will be summarized for each treatment arm. In addition, the numerical difference, and 95% CI of the difference, in the median, 25th, and 75th percentiles between the two treatment arms will be presented. Plots of the KM survival curves will be presented for the two treatment arms, unadjusted for the stratification variables. A stratified Cox proportional hazards model will be used to estimate the hazard rate ratio and the corresponding 95% CI for oral azacitidine relative to placebo.

Additionally, KM methods will be used to estimate the 1-year and 2-year survival probabilities for time to death from any cause. Estimates of the 1-year (365 days) and 2-year (730 days) survival probabilities and corresponding 95% confidence intervals will be presented by treatment arm. Kaplan Meier methods will also be used to estimate the death probabilities at 30, 90 days, 6 months and 1 year. The death rate (count and percent) at 30, 90 days, 6 months and 1 year will also be summarized.

11.2.2. Sensitivity Analysis

The primary efficacy analysis, as described above, will be repeated using the mITT population as a sensitivity analysis.

To assess the potentially confounding effects of other therapy received subsequent to the study treatment, the following additional sensitivity analysis will be performed.

1. Censoring for the use of any subsequent therapy (including post-treatment transplant) for AML. For this analysis, subjects who received any subsequent therapy for AML following discontinuation from their study drug will be censored on the earlier of first subsequent therapy date, or transplant date, regardless of their survival status at the time of the final analysis.
2. Censoring for the use of disease modifying subsequent AML therapy, which is defined as any subsequent AML therapy that is not hydroxycarbamide.
3. Censoring for post-treatment transplant. For this analysis, subjects who received post-treatment transplant will be censored at the time of the transplant.

These modified time to death endpoints will be based on the ITT population and analyzed using the same methods described previously for the primary efficacy endpoint. In addition, based on the 13 April 2018 Type C Guidance meeting with the Agency on the analysis issues with subsequent therapy, the following analyses will be performed to further investigate impacts of subsequent AML therapy on the overall survival. The following methods are planned:

- Cox proportional hazard model with covariates adjustment will include, but not limited to, subsequent AML therapy (time-varying (yes or no)); treatment-by-subsequent AML therapy interaction; baseline characteristics such as age, ECOG score, cytogenetic risk status, CR/CRi status at randomization, etc. The covariates included in the final Cox model will be selected using stepwise variable selection procedure.
- Inverse probability of censoring weighted (IPCW) method. The IPCW modeling approach was introduced by Robins et al and estimates hazard ratios that are valid in the

presence of informative censoring at start of subsequent therapy. The method adjusts for subsequent therapy by recreating the population that would have been evaluated in the absence of any subsequent therapy by weighting the follow-up for those subjects who did not receive additional therapy in order to account for the follow-up of subjects who did receive subsequent therapy that has been (informatively) censored. The weights are determined by matching demographic and baseline characteristics as well as post randomization clinical factors for subjects who did and did not receive subsequent therapy. Baseline covariates include the following: age, sex, ECOG score, cytogenetic risk status at diagnosis, prior history of MDS, geographic region, CR/CRi first achieved after induction, time to first achieving CR/CRi, CR/CRi status at randomization, MRD status at randomization, with or without consolidation, # of consolidation cycles received, platelet and ANC counts. Post randomization factors include platelet count, ANC, binary indicator of history of grade 3 or 4 AE, binary indicator of occurrence of a grade 3 or 4 since last visit, time since last visit (months), bone marrow blast %, and ECOG score. Each subject is weighted equal to the inverse probability of not receiving additional treatment. Adjusted HRs for the treatment effect are then estimated from Cox regression models with adjustment for subsequent therapy (i.e., censoring at time of subsequent therapy), both with and without further adjustment for baseline covariates.

- Regression based imputation analysis method proposed by Luo, X. et el that allows for inferences about the treatment effect in the presence of confounding due to additional therapy received subsequent to the study treatment. This method provides adjusted estimates of the KM survival curves, which allows for comparisons using the log-rank test and the calculation of an adjusted HR and associated confidence intervals.

At the final analysis, the assumption of proportional hazards will be tested by a time-dependent Cox model with interaction of treatment and time. A figure of hazard function over time will give an instinct idea of hazard trend over time.

If proportional hazard assumption is violated, the following sensitivity analyses will be conducted using ITT population:

1. Restricted mean survival time will be generated and compared between oral azacitidine and placebo arms;
2. Piecewise cox regression will provide hazard estimates at the following intervals, ≤ 3 months, 3 - ≤ 6 months, 6 - ≤ 12 months and > 12 months;
3. In the presence of non-proportional and early OS separation, a generalized Wilcoxon test will be utilized to compare survival curves.

To evaluate the impact of censoring in the primary analysis due to subjects who withdrew consent from survival follow-up, a sensitivity analysis of the OS endpoint will be performed. For this analysis, subjects who withdrew consent from survival follow-up will be treated as an event rather than as a censored observation. This sensitivity analysis will be based on the ITT population.

11.3. Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints will be analyzed based on ITT population. Supportive analysis for the secondary efficacy endpoints will be analyzed in mITT population.

11.3.1. Key Secondary Endpoint – Relapse-free Survival (RFS)

Primary analysis

Relapse-free survival is defined as the time from the date of randomization to the date of documented relapse or death from any cause, whichever occurs first. Subjects who are still alive without documented relapse, or who were lost to follow-up or withdrew consent without documented relapse, will be censored at the date of their last bone marrow assessment. Relapse is defined according to the IWG AML response criteria. See Appendix 17.7 for definitions of response categories. Documented relapse is defined as, the earliest date of the following

- ≥ 5% bone marrow blasts (myeloblasts) from Central Pathology report, or
- appearance of > 0% blasts in the peripheral blood with a later bone marrow confirmation (bone marrow blast [myeloblasts] ≥ 5%) within 100 days, or
- at least 2 peripheral blasts ≥ 5% within 30 days.

Peripheral blasts reported from both Central Pathology and Central lab will be considered. Subjects who withdrew for any reason or received another therapy for AML without documented relapse will be censored on the date of their last bone marrow assessment, prior to receiving any other therapy for AML. Subjects who are still on treatment at the time of study closure without documented relapse will be censored on the date of their last bone marrow assessment. These rules are based on FDA guidance for cancer trial endpoints [redacted], and table 2 specifies the application of the guidance for various common situations for the calculation of RFS.

Table 2 Primary Censoring Rules for RFS

Situation	Derivation Rules	Situation Outcome
Either documented relapse or death	Define event date is earliest of: • Date of documented relapse • Date of death Calculate interval between the event date and the previous bone marrow assessment date or the randomization date (if no post-baseline bone marrow assessment). Note: The cutoff of 200 day is selected based on the following protocol specified schedule procedure: the 28-day treatment cycle has +/- 3 days window; bone marrow is expected to be conducted every 3 cycles (with +/- 7 day window). Thus, 31*3+7=100 days is considered within the window for any two consecutive scheduled assessments.	If interval ≤ 200 days, then: **Event**, if no subsequent therapy for AML or subsequent therapy for AML is on or after event date. **Censor**, if subsequent therapy for AML is before event date. Censor date is last bone marrow assessment on or before start of subsequent therapy for AML, or randomization date if no post-baseline bone marrow assessment prior to start of subsequent therapy for AML. If interval > 200 days, then: **Censor,** Censor date is last bone marrow assessment date, or randomization date if no post-baseline bone marrow assessment prior to start of subsequent therapy for AML.
No documented relapse and no death		**Censor,** Censor date is last bone marrow assessment date, or randomization date if no post-baseline bone marrow assessment prior to start of subsequent therapy for AML.

The analysis of RFS will be performed using the ITT population and will be analyzed using the same methods as those used for the primary efficacy analysis of OS. In order to preserve the overall alpha level at 0.05 across the OS and RFS endpoints, formal statistical inference for the RFS analyses can only be made if superiority of oral azacitidine is demonstrated for the primary efficacy endpoint, OS, at the two-sided 0.05 significance level. The p-value from the stratified log-rank test will be the confirmatory p-value.

Sensitivity analysis

The analysis of the RFS endpoint will be repeated for mITT population as a supportive analysis.

Additional sensitivity analysis, based on the ITT population, will be performed using the RFS definition where documented relapse is based on investigator assessed response.

In addition, sensitivity analysis of RFS using censoring rules based on EMA guidance [redacted] will also be performed. Details of the EMA censoring rule are provided in Table 3 below.

Table 3 EMA Censoring Rules for RFS

Situation	Derivation Rules	Situation Outcome
Either documented relapse or death	Define event date is earliest of: • Date of documented relapse • Date of death	**Event,** Event date is earliest of documented relapsed date or death date.
Without documented relapse or death		**Censor** Censor date is date of last bone marrow assessment or date of randomization if no post-baseline bone marrow assessment

11.3.2. Additional Time-to-Event Secondary Efficacy Endpoints

Other time-to-event secondary efficacy endpoints will be analyzed similarly to the primary efficacy endpoint without stratification. Kaplan-Meier methods will be used to estimate time-to-event curves, unless otherwise specified.

Time to relapse

Time to relapse is defined as the time from the date of randomization to the date of documented relapse. Time to relapse will be analyzed using a competing risk analysis where death without documented relapse is treated as a competing risk for relapse. Similar censoring rules as in primary analysis of RFS will be applied. The cumulative incidence function ([redacted]) for time to relapse will be summarized and displayed graphically for each treatment arm.

Time to discontinuation from treatment

Time to discontinuation from treatment will be assessed and is defined as the interval from the date of randomization to the date of discontinuation from IP. Subjects who are ongoing in treatment at the time of study closure will be censored at the date of last visit.

Time to discontinuation from treatment will be analyzed using a competing risk model with reason for treatment discontinuation classified as:

- Disease relapse
- Adverse event(s)
- Became eligible for bone marrow or stem cell transplant
- Withdrawal of consent / lost to follow-up / protocol violation /Other
- Death

Cumulative incidence curves will be estimated and summarized for each specific reason for discontinuation from treatment by treatment arm.

11.4. Subgroup Analysis

In addition to analyses that include all ITT subjects, additional exploratory subgroup analyses will be performed where an adequate number of subjects are available in each subgroup to allow for meaningful interpretation of results. Analyses will be performed within the following subgroups for the OS and RFS endpoints:

- Age at induction therapy (< 65, ≥ 65, ≥ 75 years)
- Sex (male, female)
- Race (White, Asian, Black or Others)
- CR/CRi status at randomization (CR, CRi)
- CR/CRi status at first achieving response (CR, CRi)
- CR/CRi status at randomization and use of consolidation (CR with consolidation, CR without consolidation, CRi with consolidation, and CRi without consolidation)
- Prior history of MDS or CMML (yes, no)
- Cytogenetic risk category at induction therapy (intermediate, poor)
- MRD status at randomization (positive, negative)
- CR/CRi status at randomization and MRD status at randomization (CR with MRD positive, CR with MRD negative, CRi with MRD positive, and CRi with MRD negative)
- Consolidation therapy following induction (yes, no)
- Consolidation therapy following induction (1 or 2 cycles, 3 or 4 cycles)
- Geographic region (North America, Europe, Asia and Australia)
- ECOG performance status (0 or 1, 2 or 3)

- WHO AML classification (AML with myelodysplasia-related changes, AML with recurrent genetic abnormalities, AML not otherwise specified)
- Types of first line subsequent therapy
    - high intensity, low intensity chemotherapy
    - hypomethylating agent (HMA) monotherapy, other non-HMA subsequent therapy
    - Azacitidine monotherapy, other subsequent therapy (excluding decitabine monotherapy)

Overall Survival and RFS will be analyzed separately within each subgroup that is of adequate size using KM and Cox proportional hazard methods as described in previous section, but without stratification. The HRs from the subgroup analyses will be displayed graphically in a Forest plot.

In addition, to explore the efficacy of oral azacitidine in subjects who have dose escalation to 300mg x 21/28 days, OS and RFS from randomization will be analyzed in this subset of subjects. The overall response (CR+CRi+Partial Remission) and corresponding best response categories (CR, CRi and PR) achieved during the dose escalation period will also be summarized in this subset of subjects. The response will be derived programmatically based on the IWG AML response criterion using clinical data.

[redacted]

[redacted]

12. SAFETY ANALYSIS

All analyses of safety data will be conducted using the safety population, which are subjects who received at least 1 dose of study drug. All safety summaries will be provided by treatment arms.

For summaries of safety data, the on-treatment period is defined as the period from date of first dose of IP through the date of last dose of IP plus 28 days, inclusive. Post-treatment period is defined as the period beyond the 28 days after the date of the last dose of IP.

By subject listings of all AEs, Treatment-emergent Adverse Events (TEAEs, as defined below in section 12.1), serious TEAEs, grade 3 or 4 TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose interruption, TEAEs leading to dose reduction and dose interruption, TEAEs leading to death, AEs during pre-treatment period, and all deaths will be provided.

12.1. Adverse Events

Adverse events (AEs) will be coded according to MedDRA, version 22. The severity of AEs will be assessed by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For any AE not listed in the CTCAE grading system, the severity of these events will be assessed by the Investigator using a 5-point scale: “Grade 1/Mild,” “Grade 2/Moderate,” “Grade 3/Severe,” “Grade 4/Life-threatening,” or “Grade 5/Death.” TEAEs with a missing severity will be presented in the summary table as an severity category of “Missing.” Relationship of AEs to investigational product by the investigator is documented on the eCRF. Adverse events that are missing the relationship to study medication will be presented in the summary table as “treatment-related”. The imputed values for relationship to study drug will be used for incidence summaries while actual values will be presented in data listings.

Treatment-emergent adverse events (TEAEs) include adverse events that started between the first dose date and 28 days after the last dose date of study treatment. Alternative definition of TEAEs will also be defined from first dose date to 28 days after the last dose date of study treatment, or date of start of subsequent AML therapy, whichever is earlier. This definition is employed to better differentiate the incidence of TEAEs between oral azacitidine and placebo without potential attenuation of differences due to events that occur in both arms due to subsequent therapies (that may have initiated prior to 28 days post last dose of study treatment).

Adverse events will be summarized by system organ class, preferred term, and treatment arm. Adverse event summaries will include frequency tables of:

- Summary of TEAEs;
- TEAEs;
- TEAEs by decreasing order of frequency of PT;
- TEAEs by decreasing order of frequency of system organ class;
- TEAEs with most frequent preferred terms (≥ 10% in the oral azacitidine group);
- Any occurrence of TEAEs by cycle of onset;

- Any occurrence of TEAEs by cycle day of onset;
- First occurrence of TEAEs by cycle of onset;
- First occurrence of TEAEs by cycle day of onset;
- TEAEs by maximum severity;
- TEAEs with severity of grade 3 or 4;
- TEAE with severity of grade 1 or 2;
- TEAEs leading to death;
- TEAEs related to study medication;
- TEAEs related to study medication with severity of grade 3 or 4;
- TEAEs related to study medication leading to death;
- serious TEAES;
- serious TEAEs by decreasing order of frequency of PT;
- serious TEAEs related to study medication;
- serious TEAEs with severity of grade 3 or 4;
- serious TEAEs related to study medication with severity of grade 3 or 4;
- TEAEs leading to study medication discontinuation;
- TEAEs leading to dose reduction of study medication;
- TEAEs leading to dose interruption of study medication;
- TEAEs leading to dose interruption and reduction of study medication;
- TEAEs by sex;
- TEAEs by age group (< 65, ≥ 65 to 75, and ≥ 75years);
- TEAEs by race group (White, Asian, Black or Others);
- TEAEs by ECOG performance status (0 or 1, 2 or 3)

Additionally, the incidence rate per 100 person-years will be summarized for all TEAEs and Grade 3 or 4 TEAEs by system organ class, preferred term, and treatment arm. The incidence rate per 100 person-years is calculated as (100*n)/*T, where n is the number of subjects with the given AE at the system organ class or preferred term level, and T is total person-years of exposure. If a subject has multiple events with the same preferred term, then the time to the first event is used. For subject with no event, time to earlier of last dose + 28 days or death date is used.

Subjects with multiple events reported for the same preferred term will be counted only once per system organ class and preferred term level. For summaries by severity (CTCAE grade), subjects with multiple events at the preferred term level will be counted once and for the highest reported severity. For summaries by treatment cycle, subjects with multiple events reported with

a start date within the same cycle for the same preferred term will be counted once per system organ class level and preferred term level within the cycle.

In summaries of TEAEs related to study medication, if a subject reports multiple occurrences of the same AE, only the related occurrence will be summarized. Adverse events with missing relationship to study medication will be imputed as related to study medication.

Additional safety analysis may be performed, displayed and summarized, when deemed necessary.

To assess the safety profile among subjects who have dose escalation, defined as subjects who have at least one assigned dose of 300mg × 21/28 days, the following summary tables will be provided in subjects with dose escalation:

- First occurrence of TEAE by dose schedule period (300mg × 14/28days, 300mg × 21/28days);
- Any occurrence of TEAE by dose schedule period (300mg × 14/28days, 300mg × 21/28days);
- Exposure adjusted incidence rate of first occurrence of TEAE by dose schedule period (300mg × 14/28days, 300mg × 21/28days);
- Exposure adjusted incidence rate of any occurrence of TEAE by dose schedule period (300mg × 14/28days, 300mg × 21/28days);
- Any occurrence of TEAEs by cycle of onset

The first occurrence and any occurrence of Grade 3/4 TEAE by dose schedule period will also be summarized.

12.2. Adverse Events of Special Interest

12.2.1. Treatment-emergent Adverse Events of Special Interest

The AEs of special interest or AESIs refers to a group of terms/PTs from one or more SOCs relating to a defined medical condition or area of interest. The AE of special interest phrase or term refers to the group of PTs, rather than the individual PTs. Treatment-emergent adverse events for categories of adverse events of special interest will be selected using Standardized MedDRA Query (SMQ) definitions or MedDRA SOC and/or PT definitions. TEAEs will be summarized for the following categories of AESIs PT and by treatment arm:

- Myelosuppression
  - Neutropenia
  - Thrombocytopenia
  - Anemia
  - General myelosuppression;
- Hemorrhagic events
- Infections,
- Renal failure

- Hepatic failure
- Ischemic colitis
- Cardiac events
  - Cardiac arrhythmias
  - Myocardial infarction
  - Cardiac failure
- Psychiatric disorders
- Tumour lysis syndrome
- Interstitial lung disease
- Gastrointestinal Events
- Anxiety, confusional state, insomnia

Adverse events of special interest will include summary of the following:

- Summary of AESI;
- AESI and exposure adjusted incidence rate;
- AESI related to study medication;
- AESI with severity of grade 3 or 4;
- AESI related to study drug with severity of grade 3 or 4;
- AESI leading to death
- AESI leading to death by cycle of onset
- AESI related to study drug leading to death
- Serious AESI
- Serious AESI related to study drug
- AESI leading to dose reduction
- AESI related to study drug leading to dose reduction
- AESI leading to dose interruption
- AESI related to study drug leading to dose interruption
- AESI leading to dose interruption and dose reduction
- ASEI related to study drug leading to dose interruption and dose reduction
- AESI leading to study drug discontinuation;
- AESI related to study drug leading to study drug discontinuation

Each category/subcategories of adverse events of special interest defined above, with the exception of the infection and tumour lysis syndrome categories, will be summarized by AESI

category, preferred term, and treatment arm. Additionally, the incidence rate per 100 person-years will also be summarized for each event of interested.

12.2.2. Second Primary Malignancies

Second primary malignancies (SPM) will be monitored as events of interest and reported in the CRF serious adverse event for SPM page throughout a subject's duration in the study (signing of informed consent form through the follow-up period of study).

By-subject listings will be provided for SPMs and related procedures/surgeries, radiation therapies and regimen therapies.

12.3. Death

The primary cause of death verbatim term as recorded on the CRF death form will be coded according to MedDRA, version 22. The CRF death form also collects the Primary Category of Death Cause, as selected by the investigator. A summary of all deaths will be provided by treatment period, primary category of death cause by investigator, and the coded primary cause of death (by system organ class, preferred term).

An additional summary of death will be provided for ITT population.

Listings will be provided and will include all subjects who died after signing informed consent.

12.4. Clinical Laboratory Evaluations

The laboratory assessments prior to and including the date of first dose of study medication will be considered pre-treatment. The baseline value is defined as the last (most recent) non-missing value during the pre-treatment period. The laboratory data collected after date of discontinuation from the treatment period (date of last dose of IP + 28 days or end of treatment visit, whichever is longer) will be considered post-treatment.

Clinical laboratory values from the central laboratories will be graded according to CTCAE version 4.0 for selected tests (see Appendix 17.8 for list of tests). Summary statistics (N, Mean, SDev, Median, Minimum, and Maximum) of observed and change from baseline values will be presented for each lab test at each scheduled visit. Frequency distributions for shift from baseline to worst CTCAE grade observed across all cycles and within each cycle will be displayed by treatment arm for CTCAE graded tests. Clinical laboratory values with a CTCAE grade of 3 or 4, observed during treatment will be summarized (counts and percentages) by cycle for CTCAE graded tests. Listings of clinical laboratory data with abnormal flags will be provided by subject and test.

Nadirs (minimum values) of selected hematology parameters (Hgb, platelets, ANC, WBC and RBC) across all cycles and within each cycle will be summarized by cycle onset day using frequency distributions (counts and percent). Additionally, the average onset day of nadir will be summarized across all cycles using descriptive statistics. The earliest cycle day on which the lowest value was observed will be used as the onset day of the nadir. In addition, descriptive

statistics of the analyte values at nadir and change from baseline to nadir value will be provided for each selected hematology test.

Graphical display of select laboratory parameters over the course of the study will be provided.

12.5. Vital Sign Measurements

For vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature and weight), summary statistics (N, Mean, SDev, Median, Minimum, and Maximum) of observed and change from baseline values will be presented by study visit. The baseline value is defined as the last (most recent) non-missing value during the pre-treatment period. Post-treatment vital sign values will not be included in summary tables but will be included in data listings.

12.6. Electrocardiograms

A 12-lead electrocardiogram (ECG) is required for all subjects at Screening visit. Screening ECG results will be provided in a by-subject listing.

12.7. Chest X-Ray

A chest x-ray will be taken at the Screening Visit unless the subject has a previous chest x-ray taken within 4 weeks prior to Day 1 that was not clinically significant.

Screening chest x-ray information will be provided in a by-subject listing.

12.8. Pregnancy Status

A by-subject listing of pregnancy tests and results will be provided for all female subjects of childbearing potential.

14. INTERIM ANALYSIS

14.1. General Information

One interim analysis to assess futility was planned-in the protocol-when approximately 30% of the total events (99 deaths) have occurred. A beta-spending function was used to calculate a futility boundary of $Z < -1.9796$ using Gamma(-10) and corresponds to a conditional power level of approximately 18%. The interim analysis was performed with a data cutoff date of 31Dec2015, when 104 deaths occurred. The DMC meeting was held on 23 Mar 2016 where DMC members reviewed unblinded efficacy and safety data. The DMC concluded that the hazard ratio of the CC-486 over placebo remained within the protocol pre-specified futility boundary, and the AE profile did not raise any unexpected safety concerns. Therefore, the DMC recommended that the study could continue as planned.

14.2. Statistical Approaches for Control of Alpha

Because the interim analysis is for assessing futility purpose only, no alpha adjustment will be applied in the final analysis.

14.3. Data Monitoring

An independent DMC with multidisciplinary representation were established to evaluate the ongoing safety of the study subjects during the trial. The DMC comprised of medical oncologists with experience in treating subjects with AML and a statistician, all of whom are not otherwise involved in the study as investigators. The DMC met at least semi-annually after sufficient subject data has been collected. The DMC responsibilities, authorities, and procedures were documented in the DMC charter, which were endorsed by the DMC prior to the first data review meeting.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

The planned sensitivity analysis of RFS using alternative definition of documented relapse, as specified in protocol 10.6.2.1, with 16% bone marrow blast cutoff value will not be performed.

Because there is only one subject who lost to follow up from the study, the planned sensitivity analysis for RFS with modified definition as specified in protocol section 10.6.2.1 will not be performed.

17. APPENDICES

17.1. Handling of Dates

17.1.1. Dates Handling

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedures are performed. They include the dates of laboratory testing, physical examinations, bone marrow aspirate/biopsy, etc. They should be present whenever data for a protocol-specified procedure is present and should only be missing when a procedure is marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 15.1 (e.g., for duration or cycle assignment etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study termination, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the progression date is derived from the date of the bone marrow aspirate that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules (see section 5.1.2 below).

Dates recorded in comment fields will not be imputed or reported in any specific format.

17.1.2. Calculation Using dates

Calculations using dates (*e.g.*, subject's age or relative day after the first dose of study medication) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study medication (e.g,

azacitidine) plus 1 day. The generalized calculation algorithm for relative day if the following:

- If TARGET DATE >= DSTART then STUDY DAY=(TARGET DATE-DSTART)+1;
- Else use STUDY DAY=TARGET DATE-DSTART.

Note that Study Day 1 is the first day of treatment of study drug. Negative and zero study days are reflective of observations obtained during the baseline/screening period. Note: Partial date for the first study drug is not imputed in general. All efforts should be made to avoid incomplete study drug start date.

- Age (expressed in days) is calculated: AGE = CONSENT – DATE of BIRTH + 1. In practice, age will be converted to years by dividing the difference by 365.25 days, then truncating.
    - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7.
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /~~3~~30.4375.

17.1.3. Calculation of Cycles

The start date of each treatment cycle will be calculated based on study drug exposure records for each subject. The start date of the first cycle will be the earliest date the subject receives any study drug.

Once the start dates, e.g., S_1, S_2, S_3… are calculated, the end date of each cycle is calculated as the day before the start date of the following cycle, i.e., $E_i = S_{i+1} - 1$. For the last cycle, the end date will be the same as the treatment end date, which is calculated as the last dose date +14 days (the prescribed rest period of each cycle), or the death date, whichever is earlier.

The cycle number for each data of interest, e.g., AE or lab, will be calculated based on the cycle window set by their start and end dates. If a date is on or after S_i and before S_{i+1}, the corresponding cycle number will be i.

17.2. Date Imputation Guideline

17.2.1. Impute Missing Adverse Events/ Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.

- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

17.3. Table of Events

Procedure	Pre-Randomization Phase	Double-blind Treatment Phase							Post-Treatment Follow-up Phase	
			Cycle 1		Cycle 2		Cycle 3 and Beyond			
	Visit 1/Screen (Day -28 to -1)[1]	Random-ization	Day 1[1]	Day 8, 15, 22 (± 3 days)	Day 1 (± 3 days)	Day 8, 15, 22 (± 3 days)	Day 1 (± 3 days)	Day 15[30] (± 3 days)	Treat-ment Discontin-uation	Follow -up[28]
Study Entry Assessments										
Informed Consent	×	--	--	--	--	--	--	--	--	--
Demographics & Medical History	×	--	--	--	--	--	--	--	--	--
AML Diagnosis History	×[2]	--	--	--	--	--	--	--	--	--
Transplant Eligibility	×	--	--	--	--	--	--	--	--	--
Documentation of Induction ± Consolidation Therapies	×	--	--	--	--	--	--	--	--	--
CR/CRi Status Confirmation	×	--	--	--	--	--	--	--	--	--
12-Lead ECG	×[3]	--	--	--	--	--	--	--	--	--
Chest X-ray	×[4]	--	--	--	--	--	--	--	--	--
Prior Medications	×[5]	--	--	--	--	--	--	--	--	--
ECOG Performance Status	×	×[6]	×	--	×	--	×	--	--	--
Coagulation[7]	×	--	--	--	--	--	--	--	--	--
Serum EPO Level	×	--	--	--	--	--	--	--	--	--
Urinalysis[8]	×	--	--	--	--	--	--	--	--	--
Inclusion/Exclusion Criteria	×	--	--	--	--	--	--	--	--	--

Table 3: Table of Events (Continued)

Procedure	Pre-Randomization Phase	Double-blind Treatment Phase							Post-Treatment Follow-up Phase	
			Cycle 1		Cycle 2		Cycle 3 and Beyond			
	Visit 1/Screen (Day -28 to -1)[1]	Random-ization	Day 1[1]	Day 8, 15, 22 (± 3 days)	Day 1 (± 3 days)	Day 8, 15, 22 (± 3 days)	Day 1 (± 3 days)	Day 15[30] (± 3 days)	Treat-ment Discontin-uation	Follow -up[28]
Randomization	--	×	--	--	--	--	--	--	--	--
Safety Assessments										
Adverse Events	After signing ICD and until 28 days after the last IP dose or until the last study visit, whichever period is longer									
Second Primary Malignancy[9]	After signing ICD and throughout the duration of the study including post treatment follow-up period									
Physical Examination	×	--	×	--	×	--	×	--	×	--
Vital Signs and Body Weight[10]	×	--	×	--	×	--	×	--	×	--
Hematology[11]	×	--	×	×	×	×	×	×	×	--
Serum Ferritin[12]	×	--	×[12]	--	--	--	--	--	×	--
Unstained Peripheral Blood Smear[13]	×	--	×	×	×	×	×	×	×	--
Serum Chemistry[14]	×	--	×	--	×	--	×	--	×	--
Pregnancy Testing (FCBP only)[15]	×	--	×	--	×	--	×	--	×	--
Concomitant Medications, Therapy & Procedures[16]	--	--	×	×	×	×	×	×	×	--
Efficacy Assessments										
Bone Marrow Aspirate[17]	×	--	--	--	--	--	×	--	×	--
Bone Marrow Biopsy[17, 18]	×	--	--	--	--	--	×	--	×	--
Cytogenetic Testing[19]	×	--	--	--	--	--	×	--	×	--
Peripheral Blood Smear[20]	×	--	--	--	--	--	×	--	×	--

Table 3: Table of Events (Continued)

Procedure	Pre-Randomization Phase	Double-blind Treatment Phase							Post-Treatment Follow-up Phase	
			Cycle 1		Cycle 2		Cycle 3 and Beyond			
	Visit 1/Screen (Day -28 to -1)[1]	Random-ization	Day 1[1]	Day 8, 15, 22 (± 3 days)	Day 1 (± 3 days)	Day 8, 15, 22 (± 3 days)	Day 1 (± 3 days)	Day 15[30] (± 3 days)	Treat-ment Discontin-uation	Follow-up[28]
IWG Response Assessment[21]	--	--	--	--	--	--	×	--	×	--
Follow-up AML Relapse[22]	--	--	--	--	--	--	--	--	--	×
Follow-up AML Therapies[22]	--	--	--	--	--	--	--	--	--	×
Survival Follow-up[22]	--	--	--	--	--	--	--	--	--	×
Investigational Product (IP)										
Dispense/Administer			×[23, 24]		×[23, 24]		×[23, 24]			
IP Accountability					×		×		×	
Other Assessments										
[redacted]										
Patient-reported HRQoL Outcomes (FACIT-Fatigue Scale and EQ-5D)[25]	--	--	×	--	×	--	×	--	×	--
Healthcare Resource Utilization	After signing ICD and until 28 days after the last IP dose or until the date of last study visit, whichever is later (not collected during follow-up period).									
[redacted]										
[redacted]										-

AE = adverse event; AML = acute myeloid leukemia; ANC = absolute neutrophil count; CR = complete response; CRF = case report form; CRi = complete response with incomplete blood count recovery; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EPO = erythropoietin; FACIT -Fatigue Scale = Functional Assessment of Chronic Illness Therapy – Fatigue Scale FCBP = female of childbearing potential; HRQoL = health-related quality of life; ICD = Informed Consent Document; IP = investigational product; IWG = international working group; SAE = serious adverse event; SPM = second primary malignancy

1. Results obtained on Day 1 just prior to the first dose will serve as the Baseline values. If not available, the most recent screening results prior to Day 1 will be considered the Baseline values. Subjects who fail eligibility criteria due to low neutrophil count or platelet count or other laboratory abnormality can be re-screened as long as this occurs within 4 months (± 7 days) from the achievement of CR or CRi status.
2. Documentation of AML diagnosis will be assessed locally from bone marrow aspirate and/or biopsy sample slides.
3. Electrocardiogram required during screening period and whenever clinically indicated during the double-blind treatment phase. For subjects with an abnormal ECG, a cardiac consultation should be obtained as deemed necessary by the treating physician.
4. Chest x-ray not needed if a previous chest x-ray taken within 4 weeks prior to Cycle 1, Day 1 is available and not clinically significant.
5. Includes any prior chemotherapy, cytotoxic therapy, radiation therapy, and all medications used for the 4-week period prior to Day 1 of Cycle 1.
6. Subjects must satisfy the ECOG performance status of 0, 1, 2, or 3 to be enrolled in the study. Can be performed at randomization or Day 1 of Cycle 1.
7. Coagulation testing is conducted at screening and whenever clinically indicated during the double-blind treatment phase
8. A standard urinalysis (including microscopic analysis if indicated) is required at screening and whenever clinically indicated during the double-blind treatment phase.
9. Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of AEs throughout the duration of the study including follow-up period. Investigators are to report any SPM regardless of causal relationship to IP, occurring at any time from subject signing of informed consent document and throughout the duration of the study including follow-up period as a serious adverse event (considered to be at least "an important medical event" even if no other seriousness criteria apply). This information must also be documented on the appropriate pages of the CRF and in the subject's source documents. Documentation of the diagnosis of the SPM (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc) must be provided at the time of reporting as an SAE.
10. Includes height (at screening only), blood pressure, pulse, and temperature.
11. Includes a complete blood count (RBC count, hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], WBC count with differential, ANC, and platelet count). Any or all laboratory assessments may be repeated more frequently if clinically indicated. The samples will be collected prior to study treatment dosing and will be analyzed by the central laboratory. In the event that hematology laboratory results are needed to acutely manage the subject, local laboratory tests may be used. In addition to the local laboratory sample, a second sample should always be sent to the central laboratory.
12. Serum ferritin levels will be collected at screening, on Day 1 of Cycle 1, on Day 1 of every 3 cycles thereafter (ie, Day 1 of Cycles 4, 7, 10, 13, etc.) and at the Treatment Discontinuation visit.
13. Whenever a hematology sample is collected for a complete blood count, an unstained peripheral blood smear should be prepared and sent to the central laboratory. This unstained peripheral blood smear will be used to assess a manual blood count differential.
14. Includes serum chemistry labs (sodium, potassium, chloride, bicarbonate, calcium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, direct/indirect total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate deyhydrogenase [LDH], and uric acid). The samples will be collected prior to study treatment dosing and will be analyzed by the central laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. In the event that chemistry laboratory results are needed to acutely manage the subject, local laboratory tests may be used. In addition to the local laboratory sample, a second sample should be sent to the central laboratory.
15. A medically supervised serum pregnancy test with sensitivity of at least 25mIU/mL is to be obtained in female subjects of childbearing potential (FCBP) at Screening (within 72 hours prior to starting study therapy). A serum or urine pregnancy test (per Investigator's discretion) is to be done prior to Day 1 of every subsequent cycle (within 72 hours), and at the End of the Treatment visit. The subject may not receive investigational product until the Investigator has verified that the result of the pregnancy test is negative.
16. All concomitant over-the-counter medications, prescription medications, including anti-infectives for prophylaxis and/or treatment of an infection taken from Cycle 1, Day 1 up to 28 days after the last dose of IP or up to the Treatment Discontinuation visit, whichever period is longer, must be recorded on the appropriate page(s) of the CRF.
17. A bone marrow aspirate and biopsy should ideally be collected at Screening, no earlier than 14 days prior to randomization. The screening bone marrow aspirate and biopsy are required to be repeated even if a bone marrow aspirate and biopsy was performed for disease diagnosis/status as part of the standard of care within 28 days of Cycle 1, Day 1. The bone marrow aspirate slide, bone marrow biopsy slide, bone marrow aspirate sample for cytogenetics testing/chromosome analysis, and unstained peripheral blood smear slides must be sent to the central laboratory for review by the central pathology reviewer.

In addition, bone marrow aspirates must be collected during double-blind treatment phase on Day 1 (± 7 days) of Cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and the Treatment Discontinuation visit, in order to confirm continued CR or CRi, relapse after CR or CRi (as assessed by the Investigator based on CBC with WBC differential results), or disease relapse. After Cycle 36 bone marrow assessment for disease relapse is performed only if clinically indicated. If disease relapse features are observed following a bone marrow aspirate, it is recommended that a repeat bone marrow aspirate be performed at least 3-4 weeks later to confirm disease relapse unless the blast count was greater than 50% in the marrow or peripheral blood. Additional aspirates may be collected if clinically indicated or required for toxicity assessment. A bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice. A bone marrow biopsy may be needed to evaluate bone marrow cellularity. Whenever a bone marrow aspirate sample is sent to the local laboratory, additional (differently prepared) bone marrow aspirate slides must be sent to the central laboratory for review by the central pathology reviewer. Instructions for submission of bone marrow samples to the central (pathology) reviewer are provided in Study Reference and/or Study Central Laboratory Manual.

18. Bone marrow biopsies may be needed to assess bone marrow status if an adequate bone marrow aspirate cannot be attained.
19. Bone marrow aspirates sample tube for cytogenetics testing/chromosome analysis to be obtained at Screening for evaluation by central laboratory to obtain karyotype. A minimum of 16 analyzable metaphases for standard banding cytogenetic analysis is recommended at Screening. During the study, repeat of bone marrow cytogenetics testing is to be completed whenever a bone marrow aspirate is obtained and in order to confirm CR, CRi, or disease relapse.
20. Whenever bone marrow aspirate (or biopsy) slides are sent to the central reviewer, a peripheral blood smear slide should also be submitted.
21. International Working Group (IWG) response assessment will be assessed at Cycles 3, 6, 9, 12, 15, and 18, 21, 24, 30, 36 and the Treatment Discontinuation visit. After Cycle 36 bone marrow assessment for disease relapse is performed only if clinically indicated. Subjects should be assessed for CR/CRi status maintenance, relapse after CR/CRi, or disease relapse.
22. All discontinued subjects, regardless of reason for discontinuation, should be followed for survival, AML relapse, AML therapies and SPM every month (± 3 days) for the first year and then every 3 months (± 14 days) until death, lost to follow-up, withdrawal of consent from further follow-up, or the end of the study. Documentation such as laboratory or pathology reports, bone marrow and/or peripheral blood reports supporting the AML relapse should be requested and collected. Subjects who are discontinued prematurely will also undergo End-of-Study procedures. The monthly and the quarterly survival follow-up can be performed via a telephone interview.
23. Investigational product should be dispensed on Day 1 of each cycle only. For Day 1 of Cycle 1, treatment should be administered within 3 days after randomization. The first dose of IP on Day 1 of each cycle should be taken only after all other study Day 1 procedures have been completed. Antiemetic medication should be administered 30 minutes prior to each IP dose.
24. Investigational product is scheduled to be taken on 1-14 days of each cycle, unless there has been a schedule modification from 14 days to 7 days of IP administration due to toxicity.
25. FACIT–Fatigue Scale, EQ-5D, and exploratory quality-of-life (QoL) (Physical Impairment Numeric Rating Scale) questionnaires, should ideally be completed prior to dosing and when feasible, prior to interaction with study personnel on Day 1 of every cycle, beginning on Day 1 of Cycle 1, and at study discontinuation.
26. Bone marrow samples for biomarker assessment are desired but optional and subject must consent to the collection of these samples. Samples should be collected when bone marrow is collected at protocol specified time points and when bone marrow is collected to confirm a response (CR or CRi) or relapse. Biomarker analysis will only be performed using these samples when sufficient bone marrow sample material remains (optimally 10-15 mL). Sample collection, processing, storage, and shipment procedures will be provided in the Study Reference and/or Study Central Laboratory Manual.
27. Mandatory sample collection for PK. Subjects should consent to the collection of these samples by signing the ICD, mandatory sample collection section. Two blood samples (3 mL/sample) for azacitidine PK assessment will be collected at least 2 hours apart on Day 1 of Cycles 1, 3, and 6 between 0.5 and 6.0 hours post IP administration. Blood samples must be processed and plasma harvested and stored according to the instructions in the Study Reference and/or Study Central Laboratory Manual.
28. The study visit window in the double-blind treatment phase is ± 3 days for Cycles 1, 2, 3 and beyond, unless noted otherwise for a particular assessment. Study visits should also take into account the subject's IP supply. Only 1 cycle of IP will be dispensed to the subject on Day 1 of each cycle. Day 1 of Cycles 2 and beyond may be delayed from Day 28 of the prior cycle in order for subjects to recover from toxicity and meet criteria for re-treatment. During follow-up, the study visit window is ± 7 days for visits scheduled monthly (including the follow-up visit 28 days after last dose if necessary) or ± 14 days for visits scheduled every 3 months. One cycle (one month) is considered as 28 days (ie, 4 weeks).
29. Peripheral blood sampling for pharmacogenomic analysis is desired but optional and subject must consent to the collection of these samples. Samples should be collected when bone marrow is collected at protocol specified time points and must be collected on the same day as the bone marrow aspirate procedure.
30. Beginning with the Cycle 25, Day 15 visit, assessments are optional and occur only if clinically indicated at the discretion of the Investigator.

17.4. WHO Classification of Acute Myeloid Leukemia

Acute myeloid leukemia with recurrent genetic abnormalities

Acute myeloid leukemia with t(8;21)(q22;q22); (RUNX1-RUNX1T1)

Acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); (CBFB-MYH11)

Acute promyelocytic leukemia with t(15;17)(q22;q12); (PML-RARA)

Acute myeloid leukemia with t(9;11)(p22;q23); MLLT3-MLL

Acute myeloid leukemia with t(6;9)(p23q34); DEK-NUP214

Acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q26.2); RPN1-EVI1

Acute myeloid leukemia (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1

Acute myeloid leukemia with gene mutations

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasma

Acute myeloid leukemia, not otherwise categorized

Acute myeloid leukemia with minimal differentiation

Acute myeloid leukemia without maturation

Acute myeloid leukemia with maturation

Acute myelomonocytic leukemia

Acute monoblastic and monocytic leukemia

Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Source: [redacted]

17.5. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Source: [redacted]

17.6. Risk Status Based on Cytogenetics

Risk Status	Cytogenetics
Better-risk	inv(16)[1] t(16;16)[1] t(8;21)[1] t(15;17)
Intermediate-risk	Normal cytogenetics +8 t(9;11) Other non-defined
Poor-risk	Complex (≥ 3 abnormalities) -5 5q- -7 7q- 11q23 - non t(9;11) inv(3) t(3;3) t(6;9) t(9;22)[2]

1 Other abnormalities in addition to these finding do not alter risk status
2 Philadelphia+ AML t(9;22) consider managing as myeloid blast crisis in CML. These subjects are excluded from study entry.

Source: [redacted]

17.7. International Working Group AML Response Criteria

Hematologic Response According to IWG Criteria for AML	
Category	**Definition**
Morphologic Complete Remission (CR)	The following conditions should be met: • ANC > 1,000/μL; • Platelet count ≥ 100,000/μL; • The bone marrow should contain less than 5% blast cells; • Auer rods should not be detectable; • No evidence of extramedullary disease; • Independent of transfusions.
Morphologic Complete Remission with Incomplete Blood Count Recovery (CRi)	Defined as a morphologic complete remission but the ANC count may be < 1,000/μL or the platelet count may be < 100,000/μL.
Cytogenetic Complete Remission (CRc)	Defined as morphologic complete remission with a reversion to a normal karyotype.
Relapse Free Survival	Defined for patients who achieve CR/CRi, and is measured from the date of attaining leukemia free state until the date of AML relapse or death from any cause, whichever occurs first.
Disease Relapse	Relapse after CR/CRi is defined as reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy). In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from regeneration.

Source: [redacted]

17.8. Grades for select laboratory analytes based on CTCAE v4.0

The definitions in Tables 1 and 2 are based on the criteria specified in the CTCAE v4.0. In cases where the criteria for a grade are based on signs and symptoms in conjunction with lab results, the grade is based only on observed lab values. In cases where the same value of a lab result is used in defining more than one grade, the definition for the highest (worst) grade is implemented.

Table 6. Definitions for select Hematology analytes

Analyte	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hgb (anemia)	>= LLN	100 g/L - < LLN	80 g/L - < 100 g/L	65 g/L - < 80 g/L	< 65 g/L
Platelets (decreased)	>= LLN	75.0 x 10^9/L - < LLN	50.0 - < 75.0 x 10^9/L	25.0 - < 50.0 x 10^9/L	< 25.0 x 10^9/L
ANC (decreased)	>=LLN	1.5 x 10^9/L - < LLN	1.0 - < 1.5 x 10^9/L	0.5 - < 1.0 x 10^9/L	< 0.5 x 10^9/L
WBC (decreased)	>=LLN	3.0 x 10^9/L - < LLN	2.0 - < 3.0 x 10^9/L	1.0 - < 2.0 x 10^9/L	< 1.0 x 10^9/L

All values given in SI units. ND = Not defined in terms of laboratory values.

Table 7. Definitions for select Chemistry analytes

Analyte	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hypoalbuminemia (decreased albumin)	>= LLN	30 g/L - < LLN	20 g/L - < 30 g/L	< 20 g/L	ND
Alkaline Phosphatase (increased)	<= ULN	> ULN - 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin, Total (increased)	<=ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
SGPT* (AST) (increased)	<=ULN	> ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	> 20.0 x ULN
SGOT *(ALT) (increased)	<=ULN	> ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine (increased)	<=ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	> 6.0 x ULN
Hypercalcemia (increased calcium)	<=ULN	> ULN - 2.9 mmol/L	> 2.9 - 3.1 mmol/L	> 3.1 - 3.4 mmol/L	> 3.4 mmol/L
Hypocalcemia (decreased calcium)	>= LLN	2.0 mmol/L - < LLN	1.75 - < 2.0 mmol/L	1.5 - < 1.75 mmol/L	< 1.5 mmol/L
Hyperglycemia (increased glucose)	<=ULN	> ULN - 8.9 mmol/L	> 8.9 - 13.9 mmol/L	> 13.9 - 27.8 mmol/L	> 27.8 mmol/L
Hypoglycemia (decreased glucose)	>= LLN	3.0 mmol/L - < LLN	2.2 - < 3.0 mmol/L	1.7 - < 2.2 mmol/L	< 1.7 mmol/L

Analyte	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hypernatremia (increased sodium)	<=ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Hyponatremia (decreased sodium)	>= LLN	130 mmol/L - < LLN	ND	120 - < 130 mmol/L	< 120 mmol/L
Hyperkalemia (increased potassium)	<=ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypokalemia (decreased potassium)	>= LLN	ND	3.0 mmol/L - < LLN	2.5 - < 3.0 mmol/L	< 2.5 mmol/L
Hypophosphatemia (decreased phosphates)	>= LLN	0.8 mmol/L - < LLN	0.6 - < 0.8 mmol/L	0.3 - < 0.6 mmol/L	< 0.3 mmol/L
Hyperuricemia (increased uric acid)	<=ULN		ND	> ULN - 0.59 mmol/L	> 0.59 mmol/L

All values given in SI units. ND = Not defined in terms of laboratory values.
*SGPT and SGOT grades based strictly on laboratory values without consideration for presence or absence of symptoms.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Friday, 26 July 2019, 08:37 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName: [redacted]
Title: [redacted]
Date: Friday, 26 July 2019, 11:47 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName: [redacted]
Title: [redacted]
Date: Friday, 26 July 2019, 02:14 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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