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

INVESTIGATIONAL PRODUCT (IP):	Oral Azacitidine (CC-486)
PROTOCOL NUMBER:	CC-486-AML-001
DATE FINAL:	15 Aug 2012
AMENDMENT 1.0 DATE FINAL:	29 Dec 2015
AMENDMENT 2.0 DATE FINAL:	08 Nov 2018
EudraCT NUMBER:	2012-003457-28
IND NUMBER:	074618
SPONSOR NAME / ADDRESS:	Celgene Corporation [redacted]

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Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

Back-up 24 Hour Global Emergency Contact Call Center: [redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head dd mmm yyyy
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:** _____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:** _____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

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.

Indication

Maintenance therapy for acute myeloid leukemia (AML) in subjects aged 55 years and over, who are in first complete remission.

Objectives

Primary Objective

The primary objective of the study is to evaluate whether 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.

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.

Exploratory objectives

[redacted]

Study Design

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 3 phases; Pre-randomization Phase, Treatment Phase, and Follow-up Phase (Figure 1).

Pre-Randomization Phase (Screening Phase)

Screening procedures are to occur during the Pre-randomization Phase. Screening procedures are to take place within 28 days prior to randomization. Subject eligibility for randomization will be based on the documentation of achieving and maintaining CR/CRi following diagnosis and induction/consolidation treatment of AML, as verified by central pathology and cytogenetics review.

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 [redacted], who have achieved first CR/CRi status after induction therapy and with/without consolidation therapy will be eligible for randomization (within 4 months [± 7 days] of achieving first CR/CRi). The definitions of response criteria for CR or CRi are primarily those defined by the International Working Group (IWG) on AML [redacted] and are described below:

Complete Remission (CR)	Complete Remission with Incomplete Blood Count Recovery (CRi)
• < 5% of blasts in bone marrow • absence of blasts with Auer rods • absence of extramedullary disease • independent of blood transfusions • neutrophil counts > 1.0 x 10^9/L • platelet counts ≥ 100 x 10^9/L	• < 5% of blasts in bone marrow • absence of blasts with Auer rods • absence of extramedullary disease • independent of blood transfusions • neutrophil counts < 1.0 x 10^9/L or platelet counts < 100 x 10^9/L

A screening bone marrow aspirate, bone marrow biopsy and peripheral blood smear will be sent to the central pathology reviewer for analysis and confirmation of CR/CRi. A standard cytogenetic metaphase preparation will be made from the bone marrow aspirate at the central laboratory for cytogenetic analysis.

Additional screening assessments include demographics and medical history, prior treatments for AML (and other malignancy, if applicable), prior medications, Eastern Cooperative Oncology Group (ECOG) performance status (Appendix B), physical examination, vital signs, weight and height measurements, complete blood count (CBC) with differential count, blood chemistry, serum erythropoietin (EPO) level, urinalysis, coagulation screening, serum ferritin level, pregnancy testing (females of childbearing potential [FCBP] only), electrocardiogram (ECG), chest x-ray, transplant eligibility, documentation of induction and consolidation therapies, healthcare resource utilization and bone marrow and peripheral blood sampling for biomarker analysis. Adverse events (AEs), including second primary malignancies (SPMs) will be collected beginning on the date of signed informed consent document (ICD).

Randomization and Double-blind Treatment Phase

Following confirmation of eligibility at screening, 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). Randomization must occur within 4 months (± 7 days) of achieving CR/CRi.

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 ingest investigational product (IP) (azacitidine tablets or placebo tablets) a once a day in a fed or fasted state on the first 14 days of each 28-day cycle (Section 8.2.3 for details). Dose modifications may occur for managing toxicity or disease progression if necessary during treatment (Section 8.2.5).

During the double-blind treatment phase, subjects will be assessed for safety, tolerability and efficacy. Assessments during the double-blind treatment phase will include monitoring for AEs, monitoring for relapse of AML and SPMs, physical examination, vital signs and weight measurement, ECOG performance status, hematology and serum chemistry, serum ferritin level, pregnancy testing (FCBP only), concomitant medications, therapies and procedures, review of bone marrow aspirate (or biopsy if adequate aspirate is not attainable) and peripheral blood smear slides, cytogenetic analysis, assessing hematological response/improvement, CR/CRi status assessment, bone marrow and peripheral blood sampling for biomarker analysis, peripheral blood sampling for pharmacokinetics (PK) analysis, IP administration and accountability, HRQoL, and healthcare resource utilization.

A separate central review of all bone marrow aspirates, bone marrow biopsies, and peripheral blood smears will be conducted by a pathologist blinded to subject treatment. The central reviewer's assessments will be used to confirm the CR/CRi status at screening and during treatment for maintenance assessment. If the central reviewer and local pathologist disagree on the CR/CRi status of a subject, a third party reviewer will adjudicate and make the final assessment.

The central cytogenetic review will provide standardized analysis and reporting for all subjects, regardless of the laboratory performing the initial analysis (local or central).

CR/CRi Status Assessment

First status assessment for maintenance of CR/CRi will occur at Cycle 3. If CR/CRi status is maintained, subjects can continue on to Cycle 4 and beyond. Subjects will be further assessed for CR/CRi status at Cycles 6, 9, 12, 15, 18, 21, 24, 30, 36 and the Treatment Discontinuation visit. After Cycle 36, bone marrow evaluation for the assessment of maintenance of CR/CRi will occur only if clinically indicated at the discretion of the Investigator. Subjects may be discontinued from treatment at the Investigator's discretion for any of the reasons detailed in Section 12.

Dose and Schedule Adjustment in Subjects with Disease Relapse/Progression

In subjects on study who have subsequent evidence of disease relapse with blasts > 5% either in the peripheral blood count or bone marrow, and provided the blasts are no greater than 15% in the blood or bone marrow, escalation of the dosing regimen (dose and/or schedule) can be implemented as follows (provided it is in the subject's best interest to do so as judged by the Investigator):

- Subject currently on blinded treatment with oral azacitidine 300 mg or placebo QD for 14 days - escalate schedule to oral azacitidine 300 mg or placebo QD for 21 days
- In the event that dose had previously been reduced, subject currently on blinded treatment of oral azacitidine 200 mg or placebo QD for 14 days - escalate schedule as a first step, to 21 days QD and then escalate dose to oral azacitidine or placebo to 300 mg QD for 21 days
- Subject currently on blinded treatment with oral azacitidine 200 mg or placebo QD for 7 days - escalate schedule as a first step, to oral azacitidine 200 mg or placebo QD for 14 days and then escalate dose to oral azacitidine 300 mg or placebo QD for 14 days

Subject Discontinuation from Treatment following AML Relapse

Subjects will be discontinued from treatment when they meet the following criteria:

- Appearance of > 15% blasts in the bone marrow or peripheral blood; and
- The above occurrence should be attributed to relapse following CR/CRi, and not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy).

Prior to discontinuing a subject from treatment due to AML relapse or for any other cause, the Investigator should contact the sponsor or its designee and forward appropriate supporting documents for review and discussion.

Follow-up Phase

All discontinued subjects, regardless of reason for discontinuation, should undergo Treatment Discontinuation visit procedures at the time of study discontinuation. Subjects will have a follow-up visit for the collection of AEs up to 28 days after last dose of IP 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.

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. Details for the EP are provided in Appendix K.

Study Population

This study will enroll approximately 460 subjects, aged 55 or older, with a diagnosis of *de novo* AML or AML secondary to prior myelodysplastic disease or CMML, and who have achieved first CR/CRi following induction with or without consolidation chemotherapy. Subjects who have previously achieved CR/CRi with a hypomethylating agent will be excluded from the study.

The study will be conducted at approximately 180 clinical sites worldwide.

Length of Study

The study will close once the total number of events (n=330 deaths) required for a fully powered analysis of OS have occurred. The expected duration of the study is 91 months, including a 53-month subject accrual period, followed by an additional 24-month period of treatment and/or observation. At the investigator's discretion, subjects can continue beyond 24 months of treatment or until the study closes.

The sponsor may consider closing this trial when data supporting key endpoints and objectives of the study have been analyzed. In a case where there are subjects still being administered the investigational product, and it is the opinion of the investigator(s) that those subjects would continue to receive benefit from treatment, the sponsor has chosen to initiate an extension phase (EP) to ensure drug access for patients benefiting from oral azacitidine but as well continued collection of survival information for patients on placebo and patients in Follow-up Phase at the time of unblinding.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary and/or secondary analysis, as pre-specified in the protocol, whichever is the later date.

Study Treatments

Oral Azacitidine/Placebo

Subjects will be randomized 1:1 basis to receive 300 mg oral azacitidine or placebo for the first 14 days of each 28-day treatment cycle until no longer receiving the benefit or until the end of the study.

Best Supportive Care

Best supportive care (BSC) is not a treatment regimen in this study. However, it may be used in combination with the study treatment (oral azacitidine or placebo) as deemed necessary. Best supportive care includes, but is not limited to, treatment with red blood cell (RBC) transfusions (packed red blood cell [pRBC] or whole blood), single donor or pooled donor platelet transfusions, use of erythropoiesis stimulating agent (ESAs) and other RBC hematopoietic growth factors, antibiotic, antiviral and/or antifungal therapy, granulocyte colony stimulating factors (G-CSFs) and nutritional support (Section 8.1.2)

Overview of Efficacy Assessments

The primary efficacy endpoint is OS.

The secondary efficacy endpoints include RFS, and time to relapse from CR/CRi, time to discontinuation from treatment, safety/tolerability, patient-reported outcomes utilizing the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue Scale) and the EQ-5D and measures of healthcare resource utilization. Response will be independently assessed by a collection of hematology laboratory parameters, peripheral blood smear, bone marrow aspirates or biopsies along with cytogenetic information (if applicable).

Overview of Safety Assessments

Safety assessments include adverse events, monitoring of SPM, hematology [complete blood count (CBC) with differential] and serum blood chemistry analyses, body weight measurement, physical exam, vital signs, pregnancy testing (for FCBP subjects) and concomitant medication/therapy. Urinalysis, ECG and coagulation will be repeated whenever clinically indicated during the double-blind treatment phase.

Overview of Health-Related Quality of Life and Healthcare Resource Utilization Assessments

[redacted]

Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) with multi-disciplinary representation will evaluate safety, futility and compliance prospectively. The DMC will be comprised of medical hematologists/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 responsibilities, authorities, and procedures will be documented in the DMC charter, which will be endorsed by the DMC prior to the first DMC data review meeting. An external/independent statistician will generate critical safety reports on an unblinded basis for the DMC to review periodically. The DMC chairman may convene formal DMC meetings if there are safety concerns. The sponsor can also request additional DMC review of safety data in case of emerging safety concerns. The DMC responsibilities, authorities, and procedures will be detailed in the DMC charter which will be signed by DMC members before the first DMC data review meeting.

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The primary objective of the study is to evaluate whether maintenance therapy with oral azacitidine improves OS compared with placebo in subjects with AML, age ≥ 55 years, who have achieved first CR or CRi after induction with intensive chemotherapy with or without consolidation chemotherapy.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To determine 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.

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

The primary endpoint of the study is OS.

3.2. Secondary Endpoint(s)

The secondary endpoints of the study are:

- RFS;
- Time to relapse from CR/CRi;
- Time to discontinuation from treatment;
- Safety / tolerability (type, frequency, severity, and relationship of AEs to study treatments; physical examinations, vital signs; clinical laboratory evaluations, and concomitant medication/therapy);
- Patient-reported outcomes utilizing the FACIT-Fatigue Scale and the EQ-5D; and
- Measures of healthcare resource utilization.

[redacted]

4. OVERALL STUDY DESIGN

4.1. Study Design

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 MDS or CMML, aged ≥ 55 years, who are in first CR/CRi following induction therapy with or without consolidation chemotherapy.

The study consists of 3 phases; the Pre-randomization Phase (Screening Phase), the Treatment Phase, and the Follow-up Phase (Figure 1).

The study is amended to include an Extension Phase (EP). The EP allows subjects who are currently receiving oral azacitidine and who are demonstrating clinical benefit as assessed by the Investigator, to continue receive oral azacitidine after unblinding by Sponsor (Celgene Corporation) until they meet the criteria for study discontinuation or until oral azacitidine becomes commercially available and reimbursed. In addition, all subjects in the placebo arm and subjects who had been discontinued from the treatment phase (irrespective of randomization arm) and continuing in the Follow-up Phase will be followed for survival in the EP.

Details for the EP are provided in Appendix K.

Pre-Randomization Phase (Screening Phase)

Subject screening procedures are to occur during the Pre-randomization Phase. Screening procedures are to take place within 28 days prior to randomization. Subject eligibility for randomization will be based on the documentation of achieving CR/CRi following diagnosis and induction/consolidation treatment of AML, as verified by central pathology and cytogenetics review.

Newly diagnosed subjects, ≥ 55 years of age, who have a confirmed diagnosis of AML according to criteria set by the WHO 2008 classification ([redacted]) and have achieved first CR/CRi status after induction with or without consolidation therapy, will be eligible for randomization (within 4 months [± 7 days] of achieving first CR/CRi). The definitions of response criteria for CR or CRi are primarily defined by IWG on AML ([redacted]; Appendix E) and are described below:

Complete Remission (CR)	Complete Remission with Incomplete Blood Count Recovery (CRi)
• < 5% blasts in bone marrow • absence of blasts with Auer rods • absence of extramedullary disease • independent of blood transfusions • neutrophil count > 1.0 x 10^9/L • platelet count ≥ 100 x 10^9/L	• < 5% blasts in bone marrow • absence of blasts with Auer rods • absence of extramedullary disease • independent of blood transfusions • neutrophil count < 1.0 x 10^9/L or platelet count < 100 x 10^9/L

A screening bone marrow aspirate, bone marrow biopsy and peripheral blood smear will be sent to the central pathology reviewer for analysis and confirmation of CR/CRi. A standard

cytogenetic metaphase preparation will be made from the bone marrow aspirate at the central laboratory for standard cytogenetic analysis.

Additional screening assessments include demographics and medical history, prior treatments for AML (and other malignancy, if applicable), prior medications, ECOG performance status (Appendix B), vital signs, weight and height measurements, physical examination, CBC with differential count, blood chemistry, serum EPO level, urinalysis, coagulation, ECG, serum ferritin level, pregnancy testing (FCBP only), chest x-ray, transplant eligibility, documentation of induction and consolidation therapies, healthcare resource utilization and bone marrow and peripheral blood sampling for biomarker analysis. All laboratory analyses will be performed by a central laboratory. Adverse Events, including SPMs, will be collected beginning on the date of signed ICD.

Randomization and Double-blind Treatment Phase

Following confirmation of eligibility at screening, subjects will be randomized 1:1 to receive 300 mg oral azacitidine (QD) or placebo. Treatment assignment will occur by a central randomization procedure using an Interactive Voice Response System (IVRS). Randomization must occur within 4 months (± 7 days) of achieving the first CR/CRi.

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 ingest IP (azacitidine tablets or placebo tablets) on the first 14 days of each 28-day cycle. Dose modifications may occur for managing toxicity if necessary during treatment (Section 8.2.5).

During the double-blind treatment phase, subjects will be assessed for safety, tolerability and efficacy. Assessments during the double-blind treatment phase will include monitoring for AEs, monitoring for relapse of AML and SPMs, physical examination, vital signs and weight measurement, ECOG performance status, hematology and serum chemistry, serum ferritin level, pregnancy testing (FCBP only), concomitant medications, therapies and procedures, review of bone marrow aspirate (or biopsy if adequate aspirate is not attainable) and peripheral blood smear slides, cytogenetic analysis, CR/CRi status assessment, bone marrow and peripheral blood sampling for biomarker analysis, blood sampling for PK analysis, IP administration and accountability, HRQoL, and healthcare resource utilization.

A separate central review of all bone marrow aspirates, bone marrow biopsies, and peripheral blood smears will be conducted by a pathologist blinded to subject treatment. The central reviewer's assessments will be used to confirm the CR/CRi status at screening and during treatment for maintenance assessment. If the central reviewer and local pathologist disagree on the CR/CRi status of a subject, a third-party reviewer will adjudicate and make the final assessment.

The central cytogenetic review will provide standardized analysis and reporting for all subjects, regardless of the laboratory performing the initial analysis (local or central).

[redacted]

CR/CRi Status Assessment

The first status assessment for maintenance of CR/CRi will occur at Cycle 3. If CR/CRi status is maintained, subjects can continue on to Cycle 4 and beyond. Subjects will be further assessed for CR/CRi status at Cycles 6, 9, 12, 15, 18, 21, 24, 30, 36, and the Treatment Discontinuation visit. After Cycle 36, bone marrow evaluation for the assessment of maintenance of CR/CRi will occur only if clinically indicated at the discretion of the Investigator. Subjects may be discontinued from treatment at the Investigator's discretion for any of the reasons detailed in Section 12.

Dose and Schedule Adjustment in Subjects with AML Relapse/Progression

In subjects on study who have subsequent evidence of AML relapse with blasts > 5% either in the peripheral blood or bone marrow, and provided the blasts are no greater than 15% in the blood or bone marrow, escalation of the dosing regimen (dose and/or schedule) can be implemented as follows (provided it is in the best interest to do so as judged by the Investigator):

- Subject currently on blinded treatment of oral azacitidine 300 mg or placebo QD for 14 days - escalate schedule to oral azacitidine 300 mg or placebo QD for 21 days
- In the event that dose had previously been reduced, subject currently on blinded treatment of oral azacitidine 200 mg or placebo QD for 14 days - escalate schedule as a first step, to 21 days QD and then escalate dose to oral azacitidine or placebo to 300 mg QD for 21 days
- Subject currently on blinded treatment for oral azacitidine 200 mg or placebo QD for 7 days - escalate dose, as a first step, to oral azacitidine 200 mg or placebo QD for 14 days and then escalate dose schedule to oral azacitidine 300 mg or placebo QD for 14 days

Subject Discontinuation from Treatment following AML Relapse

Subjects will be discontinued from treatment when they meet the following criteria.

- Appearance of > 15% blasts in the bone marrow or peripheral blood; and

- The above occurrence should be attributed to relapse following CR/CRi, and not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy).

Prior to discontinuing a subject from treatment due to AML relapse or for any other cause, the Investigator should contact the sponsor or its designee and forward appropriate supporting documents for review and discussion.

Follow-up Phase

All discontinued subjects, regardless of reason for discontinuation, should undergo Treatment Discontinuation visit procedures at the time of study discontinuation. Subjects will have a follow-up visit for the collection of AEs up to 28 days after last dose of IP or up to the Treatment Discontinuation visit, whichever is longer. After this follow-up visit, subjects will be followed for survival 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.

Extension Phase

Details for the EP are provided in Appendix K.

Study Population

This study will enroll approximately 460 subjects, aged 55 years or older, with a diagnosis of *de novo* AML or AML secondary to prior myelodysplastic disease or CMML, and who have achieved a first CR/CRi following induction with or without consolidation chemotherapy. Subjects who have previously achieved a CR/CRi with a hypomethylating agent will be excluded from the study.

The study will be conducted at approximately 180 clinical sites worldwide.

Length of Study and Study Closure

The study will close once the total number of events (n=330 deaths) required for a fully powered analysis of OS have occurred. The expected duration of the study is 91 months, including a 53-month subject accrual period, followed by an additional 24 months of treatment and/or observation. At the Investigator's discretion, subjects can continue beyond 24 months of treatment or until the study closes.

The sponsor may consider closing this study when data supporting key endpoints and objectives of the study have been analyzed. In a case where there are subjects still being administered the investigational product, and it is the opinion of the investigator(s) that those subjects would continue to receive benefit from treatment, the sponsor may choose to initiate an extension phase under current protocol to allow those subjects to continue receiving oral azacitidine. This would occur after their participation in this study, CC-486-AML-001, and after the unblinding of those remaining subjects.

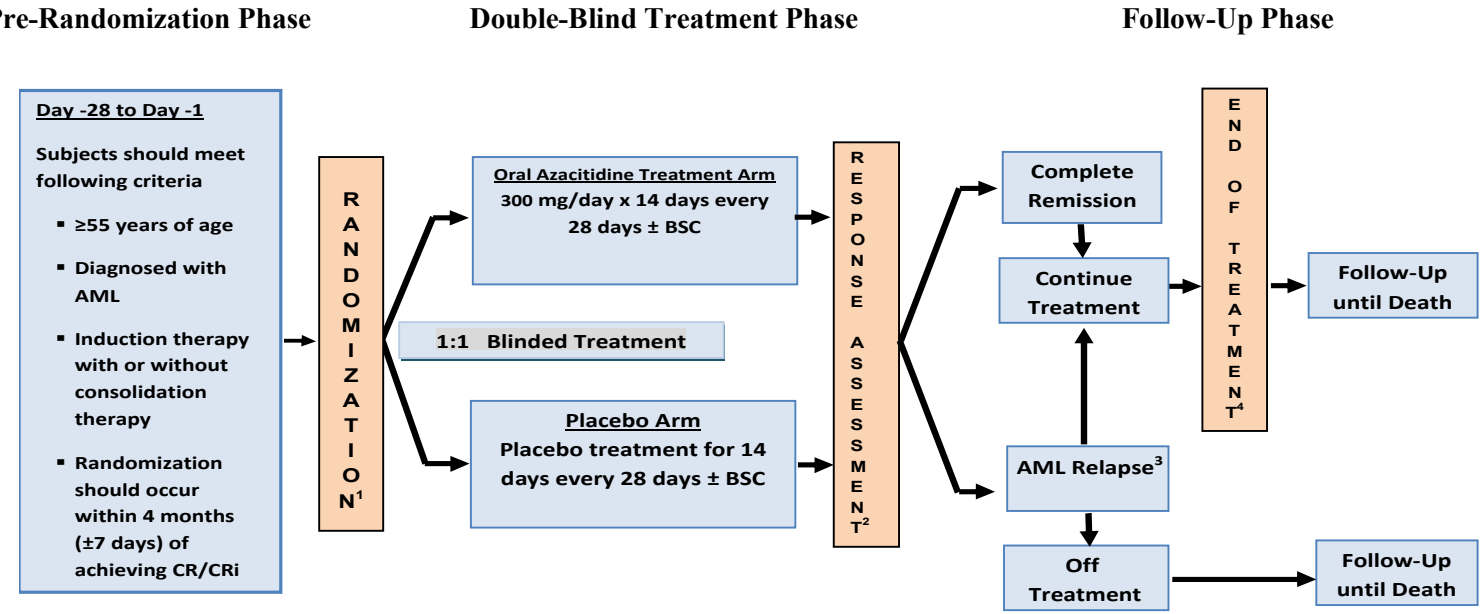
The EP of the study will close once oral azacitidine becomes commercially available and reimbursed in the participating countries for the indication that the subject is being treated for such that the subject's access to oral azacitidine is neither interrupted nor discontinued.

Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) with multi-disciplinary representation will evaluate safety, futility and compliance prospectively. The DMC will be comprised of medical hematologists/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 responsibilities, authorities, and procedures will be documented in the DMC charter, which will be endorsed by the DMC prior to the first data review meeting. An external/independent statistician will generate critical safety reports for the DMC to review periodically. The DMC chairman may convene formal DMC meetings if there are safety concerns. The sponsor can also request a DMC review of safety data. The DMC responsibilities, authorities, and procedures will be detailed in the DMC charter which will be signed by DMC members before the first DMC data review meeting.

Figure 1 provides a schematic of the overall study design.

Figure 1: Overall Study Design



AML=acute myeloid leukemia; BSC=best supportive care; CR= complete remission; CRi=complete remission with incomplete neutrophil regeneration.

[1] Stratification factors:
- [a] Age (at time of induction therapy): 55-64 and ≥ 65
- [b] Prior history of MDS: Yes / No
- [c] Cytogenetic Risk category (at time of induction therapy): Intermediate risk / Poor risk
- [d] Received consolidation therapy following induction therapy: Yes / No

[2] IWG Response Assessment for CR/CRi or Disease Relapse at Cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and the Treatment Discontinuation visit. Beyond Cycle 36, IWG assessment will be performed at the discretion of the Investigator, if clinically indicated

[3] Subjects with AML relapse (> 5% and ≤ 15% blasts in the bone marrow) may continue treatment with extended dose schedule to 300 mg QD for 21 days and discontinue treatment when the bone marrow blasts reach > 15% Section 4.1

[4] The study will close once the total number of events (n=330 deaths) required for a fully powered analysis of OS have occurred.

[redacted]

4.3. Study Duration

The study will conclude once the total number of events (n=330 deaths) required for a fully powered analysis of OS have occurred. The expected duration of the study is 91 months, including a 53-month subject enrollment period, followed by an additional 24 months of subject treatment and/or observation. At the Investigator's discretion, patients can continue beyond 24 months of treatment or until the study closes.

The sponsor may consider closing this trial when data supporting key endpoints and objectives of the study have been analyzed. In a case where there are subjects still being administered the investigational product, and it is the opinion of the investigator(s) that those subjects would continue to receive benefit from treatment, the sponsor may choose to initiate an extension phase under current protocol to allow those subjects to continue receiving oral azacitidine. This would occur after their participation in this study, CC-486-AML-001, and after the unblinding of those remaining subjects.

The EP of the study will close once oral azacitidine becomes commercially available and reimbursed in the participating countries for the indication that the subject is being treated such that the subject's access to oral azacitidine is neither interrupted nor discontinued.

5. TABLE OF EVENTS

Table 1: 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 1: 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]	Randomization	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)	Treatment Discontinuation	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 1: 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										
Pharmacokinetics[27]	--	--	x	--	--	--	X			
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).									
Optional Biomarker Bone Marrow Sampling (from the same sample taken for central review; additional consent required)[26]	×	--	--	--	--	--	×	--	x	--
Pharmacogenomic Blood Sampling[29]	×	--	--	--	--	--	×	--	x	--

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 (Appendix F), EQ-5D (Appendix G), and exploratory quality-of-life (QoL) (Physical Impairment Numeric Rating Scale, Appendix H) 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 (Section 6.11). 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 (Section 8.2.6). 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.

6. PROCEDURES

All of the required assessments are indicated in Table 1 with an "x" on the visits to be performed. All data obtained from these assessments must be present in the subject's source documentation. All routine assessments during the treatment period must be performed ± 3 days of the day indicated in the tables. 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). Procedures are described in details below and in the footnote of the Table 1.

6.1. Screening

Written informed consent must be obtained before any study-specific medical procedures are performed. Screening procedures are to occur during the screening phase (Table 1). Screening assessments must take place within 28 days prior to randomization. Samples for biomarker analyses will be collected at Screening if written informed consent is obtained.

Subject eligibility is to be established by confirming all eligibility criteria. A relevant record (eg, checklist) must be stored with the source documentation at the study site. Failure to meet any eligibility criterion excludes a subject from enrollment into the study. 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.

Prior Medical History on AML Diagnosis

History of AML disease diagnosis determined on local pathology and cytogenetics review must be collected and documented in the CRF page. Relevant medical history and current medical conditions, including those symptoms and CR/CRi status related to AML, must be recorded on the appropriate CRF at Screening. History of prior malignancy and treatment(s) administered will also be recorded on the appropriate CRF.

Prior Medications and AML Treatments and CR/CRi Status

All medications taken in the 4 weeks prior to randomization should be recorded on the appropriate CRF.

All prior treatments for AML, including induction and consolidation therapies, investigational agents or any other agent(s), should be recorded on the appropriate CRF.

Also documented in the CRF page before screening is determination of CR/CRi status following induction therapy with or without consolidation therapy.

CR/CRi Status

Bone marrow aspirates and biopsies (in phosphate-buffered saline with formalin) must be collected in order to confirm CR/CRi at screening. Whenever a bone marrow aspirate sample and stained peripheral blood smear slides are sent to the local laboratory, additional (separately prepared) bone marrow aspirate slides and stained peripheral blood smear slides must be sent to the central laboratory for review by the central pathology reviewer. A bone marrow biopsy (in sodium heparin solution) must be collected if an adequate aspirate is not attainable. The

Screening bone marrow aspirate (and biopsy) samples for central pathology and cytogenetics review and the screening hematology sample for central laboratory review should ideally be collected no earlier than 14 days prior to randomization in order to allow sufficient time for central review and a repeat bone marrow assessment, if necessary. Instructions for submission of bone marrow samples to the central (pathology) reviewer are provided in the Study Reference and /or Study Central Laboratory Manual.

Hematology

Hematology assessment includes a CBC, RBC count, hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration [MCHC], white blood count (WBC) with differential, absolute neutrophil count [ANC], and platelet count). Any or all laboratory assessments may be repeated more frequently if clinically indicated. The samples will be collected prior to dosing and 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 collected and sent to the central laboratory.

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.

Serum Chemistry

Serum chemistry labs include sodium, potassium, chloride, bicarbonate, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, direct/indirect/total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and uric acid. The samples will be collected prior to dosing and 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.

ECOG Performance Status

Performance status (0, 1, 2, or 3) will be recorded on the CRF according to Table 1, and as defined by the ECOG criteria in Appendix B.

Transplant Eligibility

Only subjects deemed ineligible for allogeneic bone marrow or stem cell transplant by the Investigator are to be included in the study. The reason(s) for a subject's ineligibility should be recorded on the appropriate CRF.

Physical Examination

Information about the screening physical examination must be present in the subject's source documentation. Significant findings that are present prior to the start of treatment with IP must be included on the appropriate CRF.

Vital Signs, Body Weight and Height Measurements

Screening vital signs include blood pressure, pulse and temperature. Height will be measured at screening only.

12-Lead ECG

The screening ECG will be a 12-lead assessment. The Investigator will review the results and assess as normal, abnormal - not clinically significant, or abnormal - clinically significant, and report the abnormal finding(s) on the appropriate CRF. It is the responsibility of the Investigator to seek cardiological consultation if thought appropriate to obtain.

Urinalysis

A standard urinalysis (including microscopic analysis if indicated) is required at screening and whenever clinically indicated during the double-blind treatment phase.

Coagulation

Coagulation at screening is conducted by the central laboratory. Coagulation includes prothrombin time (PT), activated partial thromboplastin time (PTT) and international normalized ratio (INR).

Serum Ferritin

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.

Pregnancy Testing

This protocol defines FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

All FCBP must have a medically supervised screening serum pregnancy test with a sensitivity of at least 25 mIU/mL. The FCBP subjects may not receive IP until the Investigator has verified that the result of the screening pregnancy test, which must be performed within 72 hours of randomization, is negative.

Sample Collection for Biomarker Assessments

Subjects must consent to the collection of bone marrow and blood samples for biomarker analyses. Pharmacogenomic blood samples at Screening must be collected on the same day as the bone marrow aspirate procedure.

6.2. Information to be Collected on Screening Failures

The informed consent date, demographics, and reason subject did not qualify for the study will be collected for all subjects determined to be screen failures. Adverse Events experienced by screen failure subjects will be collected from the date of signing consent to the day the subject is confirmed to be a screen failure. This information will be captured in the subject's source documents and appropriate CRF(s).

6.3. Entering a Subject Into the Study

Written consent must be obtained, all the screening evaluations must be completed, and eligibility criteria must be reviewed by the sponsor prior to contacting the IVRS to randomize a subject. Once redacted data is submitted to the sponsor, the sponsor (clinical research physician or designee) will review eligibility data and notify the Investigator that they agree with the eligibility criteria and site can proceed with the enrollment. Relevant information will also be recorded on the Screening Log.

Randomization will be stratified based on the following factors:

a. Age (at time of induction therapy): 55-64 and ≥ 65
b. Prior history of MDS or CMML: Yes / No
c. Cytogenetic Risk category (at time of induction therapy): Intermediate risk / Poor risk
d. Received consolidation therapy following induction: Yes / No

Randomization will occur by a central randomization procedure. Specific contact information and instructions will be provided individually to each study site.

Randomization of a subject in the IVRS can only be performed once the sponsor (clinical research physician or designee) has reviewed the subject's screening data and has reviewed the subject's entry into the study.

6.4. Baseline

Results obtained on Day 1 of Cycle 1 (just prior to the first dose of IP) from the physical examination, vital sign measurement, weight measurement and body surface area (BSA) calculation, and hematology or serum chemistry laboratory assessment will serve as the baseline values. If not available, the most recent screening results prior to Day 1 of Cycle 1 will be considered the baseline values.

FACIT-F, EQ-5D, and Physical Impairment Numeric Rating Scale should ideally be completed prior to dosing and prior to interaction with study personnel on Day 1 of Cycle 1.

6.5. Treatments

The first dose of IP should be administered within 3 days after randomization and within 4 months (± 7 days) of achieving CR/CRi status. The subject may not receive IP for each treatment cycle until all Day 1 procedures specified in Table 1 have been completed, including physical examination, vital signs, weight, ECG, hematology, serum chemistry laboratory assessments and pregnancy test for FCBP.

IP dispensation

Investigational product should be dispensed on Day 1 of each cycle. Subjects should not receive any IP until all Day 1 assessments have been performed and the subject is confirmed to have met all criteria for continued treatment.

IP administration

Antiemetic medication (not supplied by the sponsor) should be administered 30 minutes prior to each IP dose. If there has been no nausea/vomiting, Investigator may choose to omit antiemetic

as required, provided this is clearly documented in the CRF. Investigational product is scheduled to be taken on Days 1 through 14 of each 28-day cycle. Refer to Section 8.2.3 for more information.

IP accountability

Investigational product accountability will be assessed by site personnel using pill counts and information provided by the subject or caregiver. Investigational product dosing information should be captured in the source documentation on Day 1 of each cycle beginning at Cycle 2 and at Treatment Discontinuation. Investigational product dosing information must also be entered on the appropriate CRF. Refer to Section 12 for more information.

Refer to Appendix K for Treatment Assignment, IP dispensation and IP accountability in the EP.

6.6. Safety

Safety assessments will consist of evaluating AEs and serious adverse events (SAEs) and concomitant medication/therapies used to treat them, secondary primary malignancy, hematology and serum chemistry parameters, body weight measurement, vital signs, physical examinations, and pregnancy testing (for FCBP subjects). Urinalysis and ECG will be repeated whenever clinically indicated during the double-blind treatment phase.

6.6.1. Adverse Events

All subjects will be monitored for AEs during the study. Assessments may include monitoring of the following parameters: the subject's clinical signs and symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or results of any other appropriate test or procedure.

All AEs will be recorded by the Investigator from the time the subject signs the informed consent document (ICD) to 28 days after the last dose of IP or until the date of the last study visit, whichever is later. Adverse events and SAEs must be recorded on the AE CRF and in the subject's source documentation. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile or other appropriate method, using the serious adverse event (SAE) Report Form, or approved equivalent form.

Information about common AEs of azacitidine can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information about common side effects will also be included in the subject ICD and should be discussed with the subject as needed during the study.

6.6.2. Second Primary Malignancies

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 post treatment follow-up period. Investigators are to report any second primary malignancy, regardless of causal relationship to IP, occurring at any time from signing of informed consent and until the last study visit, whichever period is longer as a SAE (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 on the diagnosis of the second primary malignancy (eg, any confirmatory

histology or cytology or pathology results, X-rays, CT scans, etc.) must be provided at the time of reporting as an SAE. Subjects will be followed for SPMs as described in Section 6.14

6.6.3. Physical Examination

Physical examinations must be performed as indicated in Table 1.

6.6.4. Vital Signs Measurement

Vital signs (blood pressure, pulse and temperature) measurements must be performed as indicated in Table 1.

6.6.5. Weight

Weight measurements must be performed as indicated in Table 1. No dose adjustment should be made for weight loss or gain alone; however, the reason for weight loss (eg, significant nausea, vomiting, anorexia, etc.) or weight gain (e.g. peripheral edema) should be investigated to determine if a dose modification is warranted.

6.6.6. Hematology and Serum Chemistry Laboratory Evaluations

Hematology and serum chemistry laboratory analyses must be performed according to Table 1. The same parameters as required at screening should be evaluated. All samples should be sent to the central laboratory. In the event that an immediate laboratory assessment is required to acutely manage a subject, local laboratory tests may be used. In addition to collecting the local laboratory sample, a second sample should be collected and sent to the central laboratory.

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

When abnormal laboratory values or test results constitute an AE (ie, induce clinical signs/symptoms, require medical intervention, or result in IP dose reduction, interruption or discontinuation) they must be recorded on the AE CRF. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant (eg, cause IP treatment modification or discontinuation), meet the criteria for a Serious Adverse Event, or require medical intervention. Any laboratory abnormality that meets one or more of these criteria should be recorded on the AE CRF using the appropriate term (ie, sign, symptom or diagnosis) associated with the event.

6.6.7. Pregnancy Testing (FCBP only)

A serum or urine pregnancy test (per Investigator's discretion) is to be done within 72 hours prior to starting study therapy in the double-blind treatment phase. The screening serum pregnancy test can be used as the test prior to starting study therapy in the double-blind treatment phase if it is performed within the 72-hour timeframe. A serum or urine pregnancy test (per Investigator's discretion) is to be done within 72 hours prior to IP administration on Day 1 of Cycle 2 and every treatment cycle thereafter, and at the Treatment Discontinuation visit. The subject may not receive IP until the Investigator has verified that the result of the pregnancy test is negative. Pregnancy testing at screening is provided in Section 6.1.

6.6.8. Concomitant medications/significant non-drug therapies/concomitant procedures

All concomitant over-the-counter medications including vitamins/minerals and herbal supplements taken for general health and well-being and prescription medications including anti-infectives for prophylaxis and/or treatment of an infection that are 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.

6.7. Efficacy

IWG Response

International Working Group response assessment will be assessed at Cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and the Treatment Discontinuation visit. After Cycle 36, IWG response assessment will be performed if clinically indicated at the discretion of the Investigator. Subjects should be assessed for CR/CRi status maintenance or disease relapse.

Bone Marrow Aspirate, Biopsy and Peripheral Blood Smear

Bone marrow aspirate (or biopsy if adequate aspirate is not attainable) samples during the double-blind treatment phase should be collected on Day 1 (± 7 days) of Cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and the Treatment Discontinuation visit. After Cycle 36, bone marrow aspiration collection and evaluation will occur if clinically indicated at the discretion of the Investigator.

Additional bone marrow samples should be collected as clinically indicated. A bone marrow biopsy must be collected if adequate aspirate is not attainable. Whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared.

Instructions for submission of bone marrow samples are provided in Study Reference and/or Study Central Laboratory Manual.

Cytogenetics

Bone marrow cytogenetic testing is to be completed whenever a bone marrow aspirate (or biopsy if adequate aspirate is not attainable - note that specific handling of the biopsy is required if to be used for cytogenetics testing [see the Study Reference and/or study's Central Laboratory Manual for handling instructions]) is obtained for efficacy assessment.

Follow-Up AML Therapies

All discontinued subjects, regardless of reason for discontinuation, should be followed for subsequent AML therapies every month for the first year and every three months thereafter until death, loss to follow-up, withdrawal of consent from further follow-up, or study closure. Subsequent AML therapy follow-up can be performed via the telephone.

Survival Follow-Up

All discontinued subjects, regardless of reason for discontinuation, should be followed for survival every month for the first year and every three months thereafter until death, lost to follow-up, withdrawal of consent from further follow-up, or study closure. The survival follow-up can be performed via telephone.

[redacted]

6.10. Health Resource Utilization

Healthcare utilization data will also be collected. Information on each hospitalization will be collected utilizing a CRF designed specifically for this purpose. Information to be collected will include, but not be limited to, the reason for hospitalization (eg, disease relapse, AML-related illness, treatment-related AE), and days of hospitalization by treatment setting (inpatient, special care unit). Other disease- and treatment-related forms of healthcare utilization will be collected through routine study activities. These include diagnostic procedures and treatment interventions not requiring hospitalization such as those required for AML-related illness, or for treatment-

related adverse events. Additionally, information on all concomitant medications and resource use associated with treatment administration for AML will be collected.

Healthcare resource utilization information should be collected after a subject signs informed consent through 28 days after the last dose of IP or until the date of last study visit, whichever is later.

[redacted]

6.12. Unscheduled Visits

Should it become necessary to repeat an evaluation (eg, laboratory tests, vital signs, etc.), the results of the repeat evaluation should be entered as appropriate in an additional unscheduled visit page of the CRF.

6.13. Discontinuation

The investigator should contact the sponsor or its designee and forward appropriate supporting documents for review and discussion prior to discontinuing a subject. All subjects who have received at least one dose of IP should undergo Treatment Discontinuation procedures when treatment is discontinued. The Treatment Discontinuation procedures include AEs, monitoring for progression of AML and SPM, physical examination, vital signs and weight measurements, ECOG performance status, hematology and serum blood chemistry, serum ferritin level, pregnancy test (FCBP only), concomitant medications, therapies and procedures, transfusions administered, disease status assessment, subsequent AML therapies, IP accountability, HRQoL, and healthcare resource utilization.

If a subject is discontinued during a regular scheduled visit, all Treatment Discontinuation procedures should be complete at that visit. If a procedure had been performed within 7 days of the Treatment Discontinuation visit, it does not need to be repeated. For bone marrow aspirate and bone marrow biopsy, if the procedures have been performed within 15 days of Treatment Discontinuation visit, these procedures do not need to be repeated.

The reason for discontinuation will be recorded in the CRF and in the source document for all randomized subjects, regardless of whether they are dosed or not. Reasons for discontinuation are provided in Section 12.

6.14. Follow-up

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for a period of 28 days following the last dose of IP or until the date of the last study visit, whichever is later, for the collection of AEs, concomitant medications, therapies and procedures, and healthcare resource utilization. Females of childbearing potential should avoid becoming pregnant for 3 months after the last dose of IP and male subjects should avoid fathering a child for 3 months after the last dose of IP.

All subjects discontinued from protocol-prescribed therapy for any reason will also be followed for survival, AML relapse, subsequent AML therapies, and SPM every month for the first year following Treatment Discontinuation and every three months thereafter until death, lost to follow-up, withdrawal of consent for further data collection, or study closure. Documentation such as laboratory or pathology reports, bone marrow and/or peripheral blood reports supporting the AML relapse should be requested and collected. The investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow-up. Survival follow-up can be performed via the telephone.

6.15. Extension Phase

Details for the EP are provided in Appendix K.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

This study will enroll approximately 460 subjects, aged 55 or older, diagnosed with AML or AML secondary to prior myelodysplastic disease or CMML, and who have achieved CR/CRi following induction with or without consolidation chemotherapy. In addition, subjects should not be eligible for allogeneic bone marrow or stem cell transplantation.

The study will be conducted at approximately 180 clinical sites across the world.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Male or female subjects ≥ 55 years of age at the time of signing the ICD;
2. Newly diagnosed, histologically confirmed *de novo* AML or AML secondary to prior myelodysplastic disease or CMML;
3. Should have undergone induction therapy with intensive chemotherapy with or without consolidation therapy;
4. Must have achieved first CR/CRi status within 4 months (± 7 days) prior to randomization, as evidenced by the following:

Complete Remission (CR)	**Complete Remission with Incomplete Blood Count Recovery (CRi)**
• < 5% blasts in bone marrow • absence of blasts with Auer rods • absence of extramedullary disease • independent of blood transfusions • peripheral neutrophil count > 1.0 x 10^9/L • platelet count ≥ 100 x 10^9/L	• < 5% blasts in bone marrow • absence of blasts with Auer rods • absence of extramedullary disease • independent of blood transfusions • peripheral neutrophil count < 1.0 x 10^9/L or platelet count < 100 x 10^9/L

5. ECOG performance status of 0, 1, 2 or 3 (Appendix B);
6. Adequate bone marrow function based on ANCs ≥ 0.5 x 10^9/L and platelet counts ≥ 20 x 10^9/L
7. Adequate organ function, defined as:
   - Serum bilirubin ≤1.5 times the upper limit of normal (ULN);
   - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 times the ULN;
   - Serum creatinine ≤ 2.5 times the ULN;

8. FCBP[1] may participate, providing they meet the following conditions:
   - Agree to practice abstinence; or
   - Agree to use at least two effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study, and for 3 months following the last dose of oral azacitidine; and
   - Have a negative serum pregnancy test (sensitivity of at least 25 mIU/mL) at screening; and
   - Have a negative serum or urine pregnancy test (Investigator's discretion) within 72 hours prior to starting study therapy in the double-blind treatment phase (note that the screening serum pregnancy test can be used as the test prior to starting study therapy in the double-blind treatment phase if it is performed within the 72-hour timeframe).
9. Male subjects with a female partner of childbearing potential must agree to practice abstinence or to the use of a physician-approved contraceptive method throughout the course of the study and avoid fathering a child during the course of the study and for 3 months following the last dose of azacitidine;
10. Understand and voluntarily sign an ICD prior to any study related assessments/procedures are conducted;
11. Able to adhere to the study visit schedule and other protocol requirements;
12. Ability to swallow study medication.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Suspected or proven acute promyelocytic leukemia (FAB M3) based on morphology, immunophenotype, molecular assay, or karyotype; or AML with previous hematologic disorder such as chronic myeloid leukemia or myeloproliferative neoplasms, excluding MDS and CMML;
2. AML associated with inv(16), t(8;21), t(16;16), t(15;17), or t(9;22) karyotypes or molecular evidence of such translocations;
3. Prior bone marrow or stem cell transplantation;
4. Have achieved CR/CRi following therapy with hypomethylating agents;
5. Received therapy with hypomethylating agents for MDS and went on to develop AML within four months of discontinuing the therapy with hypomethylating agents;
6. Proven central nervous system leukemia;
7. Candidate for allogeneic bone marrow or stem cell transplant at screening;

[1] A woman of childbearing potential is a sexually mature woman who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie has had menses at any time during the preceding 24 consecutive months).

8. Diagnosis of malignant disease within the previous 12 months (excluding basal cell carcinoma of the skin without complications, "in-situ" carcinoma of the cervix or breast, or other local malignancy excised or irradiated with a high probability of cure);
9. Unstable angina, significant cardiac arrhythmia, or New York Heart Association (NYHA) class 3 or 4 congestive heart failure (Appendix D);
10. Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment);
11. Known active viral infection with known human immunodeficiency virus (HIV) or viral hepatitis type B (HBV) or C (HCV);
12. Known or suspected hypersensitivity to azacitidine or mannitol;
13. Use of any other experimental drug or therapy within 28 days prior to Day 1 of Cycle 1;
14. Unwilling or unable to complete patient reported outcome assessments without assistance or with minimal assistance from trained site personnel and/or caregiver;
15. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study;
16. Any significant medical condition, laboratory abnormality, or psychiatric illness that would interfere or prevent the subject from participating in the study;
17. Any condition that confounds the ability to interpret data from the study;
18. Any condition causing an inability to swallow tablets;
19. Any condition that would impair absorption of the study medication (i.e. short gut, malabsorption syndrome).

7.4. Inclusion and Exclusion Criteria for EP

Refer to Appendix K for Inclusion and Exclusion Criteria in the EP of the study.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

8.1.1. Azacitidine and Placebo

Celgene Corporation will supply azacitidine 150- and/or 200-mg tablets and matching placebo tablets for oral administration. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products.

All tablets will be packaged in blister cards. Only sufficient IP for one cycle of treatment will be provided to each subject at the start of each treatment cycle. All tablets should be swallowed whole and should not be broken or chewed.

No modification of tablets is necessary to preserve blinding as both placebo and azacitidine tablets are identical in appearance.

Shelf-life evaluation of the intact blister card is ongoing. Study drug will be monitored for stability for the duration of the study.

8.1.2. Best Supportive Care

Best supportive care may be used in combination with study treatment as deemed necessary. Best supportive care in both treatment arms will include, but not limited to RBC and platelet transfusions, use of an ESA, antibiotic, antiviral, and antifungal therapy, nutritional support (Section 9.1), and granulocyte colony stimulating factors (G-CSFs) for subjects experiencing neutropenic infections (Section 9.1), thus the risk of not providing subjects with appropriate care is minimized, while providing the potential benefit of maintaining CR/CRi status.

8.2. Treatment Administration and Schedule

8.2.1. Investigational Product Treatment Schedule

Following screening, eligible subjects will be randomized to receive 300 mg oral azacitidine or matching placebo QD for 14 days of each 28-day treatment cycle as described in Section 8.2.3. In the event of toxicity, dose and schedule may be modified (see Section 8.2.5). Subjects may continue to receive the protocol-prescribed therapy for as long as they benefit from the treatment or until treatment is discontinued for reasons detailed in Section 12. The Investigator should contact the Medical Monitor and forward appropriate supporting documents for review and discussion prior to discontinuing a subject.

8.2.2. Investigational Product Dispensation

Investigational product will be dispensed on Day 1 of each treatment cycle. Only 1 cycle of IP will be dispensed to the subject on Day 1 of each treatment cycle.

The subject may not receive IP for each treatment cycle until all Day 1 procedures have been completed and all IP from the previous cycle are to be accounted for (where applicable).

For FCBP subjects, a pregnancy test must be verified negative when performed within 72 hours prior to IP administration on Day 1 of Cycle 1.

8.2.3. Investigational Product Administration

Investigational product administration will be accurately recorded including, but not limited to, date of administration, dose and any changes in dose administration (eg, interruption or reduction in dose due to an adverse event).

Investigational product is scheduled to be taken on the first 14 days of each 28-day treatment cycle, unless there has been a schedule modification of IP administration due to disease relapse or toxicity. On PK sampling days, IP will be administered by the study site personnel in the clinic. Subject will self-administer all other IP doses in the treatment phase.

Antiemetic medication (not supplied by the sponsor) may be taken 30 minutes prior to IP administration. Subject will ingest IP with approximately 240 mL (8 ounces) of room temperature water. Investigational product may be taken on an empty stomach or with food. If IP is taken in the morning, subjects may consume their usual breakfast before or after administration. The breakfast meal should not exceed approximately 600 calories; however, the actual calorie will not need to be measured or recorded. If a meal other than breakfast is consumed, a light meal (not more than 25% of a subject's usual daily calories) may be eaten before or after administration.

Refer to Section 8.6 for details regarding IP accountability.

8.2.4. Missing Doses

All efforts should be made to administer IP on all of the scheduled days of each 28-day treatment cycle. Any missed doses during that period should not be taken after the last scheduled day of administration but should be returned by the subject for IP accountability. Any vomited doses should not be repeated. Treatment should resume on the next scheduled day.

8.2.5. Dose Modifications for Toxicity

Subjects should be monitored for toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0, as a guide for the grading of severity.

If a certain level of toxicity is observed and considered by the investigator to be at least possibly related to treatment, IP dosing may be interrupted, delayed or modified. The Investigator is encouraged to contact the Medical Monitor prior to any treatment adjustment.

A maximum of one dose reduction to a daily dose of 200 mg is permitted in the event of toxicity. If toxicity persists, a maximum of one treatment schedule modification from 14 to 7 days (21 days to 14 days for those subjects whose dose schedule has been extended due to disease progression) is permitted in the event of continuing toxicity that does not respond to dose reduction. The decision to modify a subject's treatment schedule from 14 to 7 days (21 days to 14 days for those subjects whose dose schedule has been extended due to disease progression) should first be discussed with the Medical Monitor or designee. Subjects should not receive less than 200 mg IP or be scheduled to receive treatment for less than 7 days.

Subjects who have their IP dose reduced or treatment schedule modified may return to their original dose and/or schedule in a step-wise fashion upon discussion and agreement between the investigator and the Medical Monitor provided that the increased dose or treatment schedule is

tolerable and at least two additional treatment cycles have occurred since the dose reduction or treatment schedule modification. The treatment schedule should first be increased from 7 to 14 days, followed by a dose escalation step from 200 to 300 mg.

Dose Modification for Febrile Neutropenia ≥ Grade 3

Any subject who experiences febrile neutropenia (two consecutive readings of body temperature > 38.0°C for 2 h and an absolute neutrophil count < 0.5×10^9/L) can continue to receive IP uninterrupted at the discretion of the Investigator. If the febrile neutropenia episode persists for ≥4 days despite adequate/maximal antibiotic, antiviral and/or antifungal therapy, IP should be temporarily discontinued until the fever has resolved and the ANC has improved or stabilized as assessed by the Investigator. Treatment with IP at the same dose should resume no earlier than 3 days following the resolution of the fever. If a subject experiences febrile neutropenia in 2 consecutive cycles, the steps noted above should be followed, but the IP dose should be reduced to 200 mg upon resumption of treatment with IP. A treatment schedule modification from 14 to 7 days (21 days to 14 days for those subjects whose dose schedule has been extended due to disease progression) of treatment may be warranted if a subject experiences regular episode of febrile neutropenia that are deemed by the Investigator to be related to IP.

Dose Modification for Diarrhea ≥ Grade 3

It is recommended that subjects experiencing diarrhea be managed according to the guidelines provided in Appendix I. Antidiarrheal medication may be administered as prophylaxis against diarrhea and for treatment of any AEs of diarrhea. Dose modifications for diarrhea are summarized in Section 8.2.5. In patients not having problems during the first two cycles, the treating physician may discontinue use of antiemetic medications.

Dose Modification for Nausea and Vomiting ≥ Grade 3

A serotonin (5-HT^3) receptor antagonist (eg, ondansetron) (or other comparable medication) should be administered as an antiemetic approximately 30 minutes prior to administration of IP. Antiemetic medication(s) should be administered for treatment of any AEs of nausea and/or vomiting. If there has been no nausea and/or vomiting during the first two cycles, Investigator may choose to omit antiemetic as required, provided this is clearly documented in the CRF. Dose modifications for nausea and vomiting are summarized in Section 8.2.5.

Dose Modification for Renal Dysfunction and Abnormal Serum Electrolytes

If unexplained elevations of BUN and/or serum creatinine (> 20%) occur (per Investigator), the next cycle of treatment should be delayed until values return to baseline and the dose should be reduced to 200 mg in the next cycle of treatment. A schedule modification from 14 to 7 days (21 days to 14 days in those subjects whose dose schedule has been extended due to disease progression) can be made if the elevation in BUN and/or creatinine recurs in the subsequent cycle. Should similar unexplained renal disturbances subsequently persist or recur during the next cycle of treatment, study treatment should be discontinued.

Dose Modification for Other Treatment-Related Non-Hematologic Toxicity ≥ Grade 3

Any subject who experiences a treatment-related non-hematologic toxicity Grade 3 or higher that is an escalation from baseline status (prior to first IP dose) should temporarily discontinue IP treatment until the toxicity returns to Grade 2 or lower. Dose modifications for Grade 3 or higher non-hematologic toxicity are summarized in Section 8.2.5.

Dose Modification for Weight Change

No dose adjustment should be made for weight loss or gain alone; however, the reason for weight loss (eg, significant nausea, vomiting, anorexia, etc.) or weight gain (eg, peripheral edema) should be investigated and may require a dose modification as specified in Section 8.2.5.

Table 2: Guidelines for Dose Modifications

NCI-CTCAE Toxicity Grade	Action
Febrile Neutropenia (≥ Grade 3)	• Continue IP at the discretion of the Investigator – If episode persists for ≥ 4 days despite adequate / maximal antibiotic, antiviral and/or antifungal therapy, IP should be temporarily discontinued until the fever has resolved. – Resume IP at the same dose after the fever has resolved and the ANC has improved or stabilized (as assessed by the Investigator). IP should not be resumed for at least 3 days following resolution of fever. • If a subject experiences febrile neutropenia in 2 consecutive cycles, the steps noted above should be followed, but the IP dose should be reduced to 200 mg upon resumption of treatment with IP. • If subject continues to experience febrile neutropenia episodes that are deemed to be related to IP by the Investigator, a treatment schedule modification from 14 to 7 days (21 days to 14 days for those subjects whose dose schedule has been extended due to disease progression) of treatment may also be warranted. (Treatment schedule modification requires prior discussion with Medical Monitor).
Diarrhea (≥ Grade 3)	• Interrupt IP and provide adequate/maximum medical intervention • Resume IP at same dose when toxicity resolves to ≤ Grade 1 • If event reoccurs upon re-challenge or during next treatment cycle, reduce IP dose to 200 mg. • If event reoccurs at same intensity once dose is reduced to 200 mg, follow the steps above and modify treatment schedule from 14 to 7 days (21 days to 14 days for those subjects whose dose schedule has been extended due to disease progression) of IP administration. (Treatment schedule modification requires prior discussion with Medical Monitor).

Table 2: Guidelines for Dose Modifications (Continued)

NCI-CTCAE Toxicity Grade	Action
Nausea and/or Vomiting (≥ Grade 3)	• Interrupt IP and provide adequate/maximal medical intervention • Resume IP at same dose when toxicity resolves to ≤ Grade 1 • If event reoccurs upon re-challenge or at same intensity during next treatment cycle, reduce dose to 200 mg • (Treatment schedule modification requires prior discussion with Medical Monitor).
Renal Dysfunction	• For unexplained elevations of BUN and/or serum creatinine (> 20%), hold IP, if this is apparent during the IP administration phase and/or delay the start of the next cycle of treatment until values return to baseline (± 20%). Reduce IP dose in the next cycle of treatment to 200 mg. • Discontinue IP if similar unexplained renal and/or electrolyte disturbances subsequently persist or recur during the next cycle of treatment. • (Treatment schedule modification requires prior discussion with Medical Monitor).
Other ≥ Grade 3 non-hematological treatment-related AEs	• Interrupt IP dosing and provide medical intervention as appropriate • Resume IP at same dose when toxicity resolves to ≤ Grade 2 • If event reoccurs upon re-challenge or at same intensity during next treatment cycle, reduce IP dose to 200 mg • If event reoccurs at same intensity once dose is reduced to 200 mg, follow the steps above and modify treatment schedule from 14 to 7 days (21 days to 14 days for those subjects whose dose schedule has been extended due to disease progression) of IP administration. (Treatment schedule modification requires prior discussion with Medical Monitor).

AE=Adverse Event; ANC=Absolute Neutrophil Count; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; IP=Investigational Product.

8.2.6. Dose and Schedule Adjustment in Subjects with AML Relapse/Progression

In subjects on study who have subsequent evidence of AML relapse with blasts > 5% either in the peripheral blood count or bone marrow, and provided the blasts are no greater than 15% in the blood or bone marrow, escalation of the dosing regimen (dose and/or schedule) can be implemented as follows (provided it is in the best interest to do so as judged by the Investigator):

- Subject currently on blinded treatment of oral azacitidine 300 mg or placebo QD for 14 days - escalate schedule to oral azacitidine 300 mg or placebo QD for 21 days
- Subject currently on blinded treatment of oral azacitidine 200 mg or placebo QD for 14 days - escalate dose schedule, as a first step, to oral azacitidine 200 mg or placebo QD for 21 days and then escalate dose to oral azacitidine 300 mg or placebo QD for 21 days
- Subject currently on blinded treatment for oral azacitidine 200 mg or placebo QD for 7 days - escalate dose schedule, as a first step, to oral azacitidine 200 mg or placebo QD for 14 days and then escalate dose to oral azacitidine 300 mg or placebo QD for 14 days

In cases where relapse is noted within a week of starting the next cycle, and there is a desire to escalate the dose schedule during the cycle, contact the Medical Monitor to discuss this, in order to obtain the additional required IP.

8.2.7. Re-treatment Criteria

Prior to the start of each cycle, subjects will have laboratory assessments performed to evaluate organ function. In order to proceed to the next cycle, subjects must continue to meet entry criteria regarding renal and hepatic function (see Section 7.2). Thus, subjects will have laboratory assessments performed to evaluate organ function prior to starting each cycle (including Cycle 1). Because of the time it takes to obtain results from the central laboratory, samples should be collected early enough prior to starting the next cycle in order to allow sufficient time for review. In the event that immediate laboratory assessment is needed, local laboratory measurement is acceptable for starting the next cycle pending the outcome of the central laboratory assessment (ie, in addition to collecting the local laboratory sample, a second sample should be collected and sent to the central laboratory).

The start of the next cycle will be delayed if the subject does not meet entry criteria regarding renal and hepatic function. If there is a delay of more than 42 days (6 weeks) in the start of the next cycle, the Medical Monitor must be consulted. Study treatment should be discontinued if there is a delay of more than 56 days (8 weeks) in the start of the next cycle, unless, in the opinion of the investigator and the Medical Monitor, the subject is experiencing clinical benefit. Justification of the subject continuing in the study must be recorded in the source documents.

Prior to discontinuing a subject for reasons other than those listed in Section 8.2.5, the investigator should contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

8.3. Method of Treatment Assignment

Subjects approved for enrollment will be randomized to receive oral azacitidine or placebo in a 1:1 ratio. Randomization will be accomplished by an IVRS to ensure timely registration and randomization. A stratified blocked randomization schedule will be implemented.

Investigator or designated site staff will be assigned password protected, coded identification numbers that give them authorization to call into the IVRS to enroll subjects. At screening, the investigator or designated staff will call into the IVRS and provide the requested identifying information for the subject. The IVRS will then confirm the assignment of a 2-part unique subject number. The first part is the center number and the second part is one of a series of

numbers allocated to subjects at that center. Once assigned to a subject, the subject number will not be reused. If the subject is not randomized, the IVRS must be notified.

Randomization will be performed using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigators. A subject randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment groups. The randomization scheme for subjects will be reviewed and approved by the Biostatistics Group of the sponsor, Celgene Corporation. Written consent must be obtained, all the screening evaluations must be completed, and eligibility criteria must be verified by the sponsor *prior* to randomizing a subject. Then the investigator or designated staff will call the IVRS and confirm that the subject fulfills all the inclusion and exclusion criteria. The IVRS will assign a randomization number to the subject, which will be used to link the subject to a treatment group.

A stratified randomization schedule will be implemented. Subjects will be stratified by: age at time of induction therapy (55-64 years and ≥ 65 years), prior history of MDS or CMML (Yes / No), cytogenetic risk category at time of induction therapy (Intermediate risk / Poor risk) and received consolidation therapy following induction (Yes / No). The random treatment assignment will be concealed so that investigators and subjects will not know in advance the next treatment assignment.

After randomization, no crossover between the treatment arms will be permitted. Subjects may continue to receive randomized study treatment for as long as it is appropriate, provided that all protocol-specified re-treatment criteria are met.

8.4. Packaging and Labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

8.5. Clinical Supplies

The investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying study drug shipping order form. The investigator(s) or designee(s) will verify the accuracy of the information on the form and call the IVRS to register the study medication received at the site.

At the study site, all IPs will be stored according to the storage conditions described on the IP packaging label in a locked, safe area to prevent unauthorized access. The IP must be stored as directed on package label at controlled temperature and a temperature log must be maintained in the source documents.

8.6. Investigational Product Accountability and Disposal

Investigational Product accountability will be assessed by the investigator or designee. Applicable information such as lot number, tablet count and expiration date should be collected, as well as information provided by the subject or the caregiver (eg, subject dosing diary).

Investigational Product accountability should be assessed before drug dispensing for each subsequent treatment cycle in the treatment phase, starting on Day 1 of Cycle 2, and at the Treatment Discontinuation visit.

The investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study according to applicable regulatory requirements. Any unused IP must be returned by a study subject and retained by the investigative site for accountability to be conducted by a Celgene representative (or designee). If any IP is lost or damaged, its disposition should be documented. At the periodic monitoring visits, a Celgene representative (or designee) will conduct IP accountability and address any discrepancies. Upon satisfactory reconciliation of all IP, returned IP may be destroyed. At the conclusion of the study, all remaining study drug will be counted, reconciled with dispensing records, documented, and destroyed at the clinic site or allocated drug destruction location after completion of drug accountability by a Celgene representative (or designee). The Celgene representative (or designee) will ensure that a final report of drug accountability to the unit dose level (ie, tablet) is prepared and placed in both the investigator study file and the central clinical study file.

Celgene Corporation will instruct the investigator(s) on the return, disposal and destruction of IP. A copy of the site's Standard Operating Procedure (SOP) for drug destruction may be collected by the sponsor (or designee). Any revisions to a site's destruction process must be provided and approved by the sponsor (or designee) prior to implementation on this protocol. Any site without a sponsor (or designee) approved destruction SOP and process will be required to return IP to Celgene.

8.7. Investigational Product Compliance

Investigational Product will be administered by the study site personnel in the clinic on PK sampling days. Subjects will self-administer all other IP doses in the treatment phase. Documentation of dosing during treatment will be recorded in a study specific diary card. Investigational product administration diary cards will be provided by the sponsor to study site personnel, who will in turn distribute them to study subjects. Study site personnel will enter the scheduled daily doses, the number of tablets to be taken each day and any other applicable information. Study site personnel will review the dosing information with the subject (or legally authorized representative) on scheduled clinic visit days. Subjects (or legally authorized representative) will be asked to record IP dosing information and anti-emetic medication taken at home in the diary card and to bring the diary card and unused tablets in the blister card (or the blister card packaging even if it is empty) with them to scheduled clinic visits (ie, prior to the start of the next treatment cycle). A diary card and tablet compliance check will be performed by study personnel. Diary cards must be saved and kept with the source documentation. Study site personnel will perform an IP administration compliance check and record this information in the subject's source documentation and on the appropriate CRF.

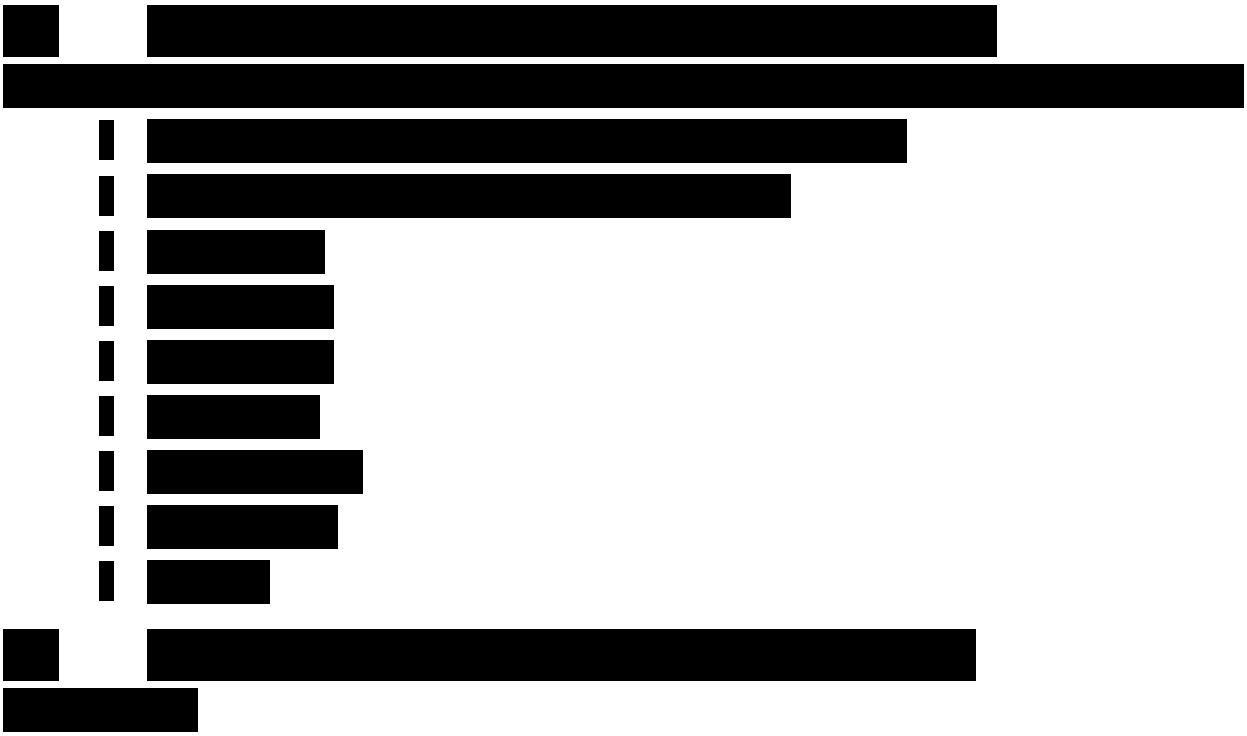
Administration of all IP will be recorded including dispensing, dosing and any changes in dosage administration such as interruption or reduction in dosing due to an AE.

8.8. Blinding

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

8.9. Emergency Unblinding

In order to maintain the integrity of the study design, the blind must not be broken during the course of the study unless, in the opinion of the investigator, it is absolutely required to safely treat the subject. There should be only rare instances when breaking the blind would be required, such as the development of pregnancy, for example. In most instances of treatment-related toxicity, interrupting treatment and/or dose reduction of IP is all that would be required. For more information on the unblinding process, please refer to Section 13.2.



10. STATISTICAL ANALYSES

10.1. Overview

This Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study is designed to compare the efficacy and safety of oral azacitidine plus best supportive care versus placebo plus best supportive care in subjects with AML who have achieved CR/CRi following induction, with or without consolidation, chemotherapy.

All data will be summarized by treatment group. In addition, where appropriate, a total column will be included to summarize subjects across treatment groups. Summaries of continuous variables will present the number of subjects included in the analysis (N), the mean and standard deviation (SD) of the mean, the median, the minimum, and the maximum statistics. Counts and percentages will be presented in summaries of categorical variables. The denominator for each percentage will be the number of subjects in the population treatment group unless otherwise specified. In general, missing data will not be imputed unless otherwise specified.

10.2. Study Population Definitions

10.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population includes all subjects who are randomized to treatment, regardless of whether they received treatment or not. All efficacy analyses will be conducted for the ITT population. Subjects will be analyzed based on randomized treatment group.

10.2.2. Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all subjects who have met all inclusion/exclusion criteria and experienced no major protocol deviations during the study, and received a minimum of one cycle of treatment. Subjects who are randomized without confirmed CR/CRi per central review will be excluded from the mITT population. This definition will be further clarified and detailed in the final statistical analysis plan prior to database lock.

Key efficacy analysis will be performed for the mITT population as supportive and/or exploratory analysis only. Subjects will be analyzed based on randomized treatment group.

10.2.3. Safety Population

The safety population includes all randomized subjects who received at least 1 dose of IP. The safety population will be used for all safety analysis. Subjects will be analyzed according to the treatment actually received.

10.3. Sample Size and Power Considerations

The equality of OS curves will be compared between the azacitidine and placebo treatment groups 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 azacitidine treated group (43% improvement), and a study duration of 60 months with a drop-out rate of 5% from both treatment groups, 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]).

10.4. Background and Demographic Characteristics

Demographic and baseline disease characteristics will be summarized by treatment group for the ITT, mITT, and safety populations. Subjects' age, height, weight, body mass index (BMI), and continuous baseline characteristics will be summarized using descriptive statistics (N, mean, SD, median, minimum, maximum), while age group, gender, race and other categorical variables will be provided using frequency tabulations (count, percent) by treatment group. Summaries of baseline disease characteristics will include CR/CRi status following induction therapy, whether the subject received consolidation therapy following induction therapy, prior history of MDS, time since initial AML diagnosis, ECOG performance status, bone marrow blasts (%), ANC (10^9/L), hemoglobin (g/dL), platelet counts (10^9/L), and cytogenetic risk classification. For laboratory and vital sign measures, the most recent assessment on or prior to the date of randomization will be used for baseline.

Medical history data (coded by the Medical Dictionary for Regulatory Affairs [MedDRA] dictionary) will be summarized using frequency tabulations by treatment group, system organ class and preferred term for the ITT, mITT, and safety populations.

10.5. Subject Disposition

Subject disposition (analysis population allocation, discontinued, along with primary reason for discontinuation) will be summarized using frequency tabulations for both treatment and follow-up phases. A summary of subjects enrolled by site and by country will be provided. Major protocol violations will be summarized using frequency tabulations for the ITT population. Supportive corresponding subject listings will also be provided.

10.6. Efficacy Analysis

All efficacy analysis will be performed on the ITT population. Key efficacy analysis will be performed on the mITT population as supportive evidence and to assess the robustness of the efficacy findings. Subjects will be analyzed according to randomized treatment group. Refer to Section 3.1 and Section 3.2 for the primary and secondary efficacy endpoints, respectively.

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 given, pre-specified order. The primary efficacy endpoint will be tested first at the two-sided 0.05 significance 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 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.

10.6.1. Primary Efficacy Analysis

The primary efficacy endpoint of OS is defined as the time from randomization to death from any cause and will be calculated using randomization date and date of death, or date of last follow-up for censored subjects. All subjects will be followed until drop-out, death, or study termination. Drop-out may be due to withdrawal of consent from further data collection or loss to follow-up. Subjects who drop-out or are alive at study termination will have their OS times censored at the time of last contact, as appropriate.

The primary efficacy analysis will be conducted for the ITT population and will compare the OS distributions between the two treatment groups. The null hypothesis for testing the primary efficacy endpoint, time to death from any cause, is that the overall survival distributions for the two treatment groups are equivalent. The OS curves will be estimated using Kaplan-Meier (KM) methods. A stratified log-rank test, stratifying by age at time of induction therapy (55-64 years, ≥ 65 years), prior history of MDS (Yes / No), whether consolidation therapy was administered (Yes / No), and cytogenetic risk category at time of induction therapy (intermediate-risk, poor-risk), at a two-sided alpha level of 0.05, will be used to compare the survival distributions between the two treatment groups. The p-value from the stratified log-rank test will be the confirmatory p-value. Kaplan-Meier estimates for median OS as well as the 25^{th} and 75^{th} percentiles and associated two-sided 95% CIs will be summarized for each treatment group, unadjusted for the stratification variables. In addition, both the numerical difference and the 95% CI of the difference, in the median, 25^{th}, and 75^{th} percentiles between the two treatment groups will be presented for the un-stratified analysis. Plots of the KM survival curves will be presented for the two treatment groups, without adjustment for the stratification variables.

A stratified Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI for 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 group.

Median follow-up time, by treatment and overall, will be estimated using KM methods. The analysis of the OS endpoint will be repeated for the mITT-population as a supportive/exploratory analysis.

In order to assess the potentially confounding effects of other cancer therapy received subsequent to the protocol therapy on the survival estimates, an exploratory analysis based on the ITT population, will be performed using modified censoring criteria. For this analysis, subjects who received subsequent therapy for AML following discontinuation from their protocol therapy will be censored on the date that the subsequent therapy was started regardless of their survival status at the time of the final analysis. This exploratory modified time-to-death endpoint will be analyzed using the same methods as described above for the primary efficacy analysis.

10.6.2. Secondary Efficacy Analyses

10.6.2.1. Key Secondary Efficacy Analyses

Relapse-free survival (RFS) is defined as the interval from the date of randomization to the date of documented relapse after CR or CRi or death from any cause, whichever occurs first. Subjects who are still alive without documented relapse after CR or CRi, or who were lost to follow-up without documented relapse, will be censored at the date of their last response assessment. Relapse after CR or CRi is defined according the IWG AML response criteria (Appendix E).

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. The p-value from the stratified log-rank test will be the confirmatory p-value.

The analysis of the RFS endpoint will be repeated for the mITT-population as a supportive/exploratory analysis. Additional sensitivity analyses, based on the ITT population, will be performed using modified RFS definitions. For these analyses of RFS, subjects lost to follow-up without documented relapse or death will be 1) considered as having an event; and 2) considered as having an event if they were randomized to the azacitidine treatment group and censored if they were randomized to the placebo treatment group. The event/censoring time will be the date of the last response assessment.

In order to assess and compare the modified definition of AML relapse being used in this protocol as criteria for discontinuation from treatment (ie, appearance of > 15% blasts in the bone marrow or peripheral blood) with respect to the IWG definition of relapse after CR or CRi (Appendix E), an exploratory analysis based on the ITT population, will be performed for RFS using this modified definition of relapse. For this analysis of RFS, relapse after CR or CRi is defined as the appearance of > 15% blasts in the bone marrow or peripheral blood. Subjects who are still alive without documented relapse after CR or CRi or who were lost to follow-up without documented relapse will be censored at the date of their last response assessment. This exploratory modified RFS endpoint will be analyzed using the same methods as described above for the key secondary efficacy analysis.

10.6.2.2. Additional Secondary Efficacy Analyses

The time-to-event secondary efficacy variables will be analyzed similarly to the primary efficacy variable without stratification. Kaplan-Meier methods will be used to estimate time-to-event curves, unless otherwise specified. Counts and percentages will be used to describe categorical secondary variables. Secondary efficacy analyses will be performed on the ITT population unless otherwise specified.

Time to relapse from CR/CRi is defined as the interval from the date of randomization to the date of documented relapse after CR or CRi, as defined according to the IWG AML response criteria (Appendix E). Time to relapse will be analyzed using a competing risk analysis where death without documented relapse is treated as a competing risk for relapse from CR/CRi. Subjects who are lost to follow-up without documented relapse or are alive at last follow-up without documented relapse will be censored at the date of their last response assessment. The cumulative incidence function for time to relapse from CR/CRi will be summarized for each treatment group. Summary statistics will include the cumulative incidence estimate of the

median time to relapse and the one-year cumulative incidence of relapse for each treatment group.

Time to discontinuation from treatment will be assessed as an estimate of treatment failure/tolerability 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
- Death

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

Additionally, time to discontinuation from treatment will be analyzed using KM methods.

10.7. Safety Analysis

All safety analyses will be performed on the safety population.

Adverse Events will be coded using MedDRA. Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent AEs (TEAEs) will be summarized by worst severity grade, system organ class, and preferred term. Treatment-emergent AEs leading to death or to discontinuation from treatment, AEs classified as CTCAE (Version 4.0) Grade 3 or Grade 4, AEs related to IP, and SAEs will be summarized separately. Time to discontinuation from the study due to AE will be summarized using KM methods. Listings of all deaths and all SAEs, regardless of when they occurred, will also be generated. Development of a SPM will be documented as an SAE (considered to be at least an "important medical event" even if no other seriousness criteria apply) throughout a subject's duration in the study (signing of ICD through the follow-up period of the study).

Clinical laboratory results will be summarized descriptively by treatment group, which will also include a display of change from baseline. Laboratory values outside of the normal ranges will be identified. Clinically significant hematologic and non-hematologic laboratory abnormalities that meet Grade 3 or Grade 4 criteria according to the CTCAE will be listed and summarized. Graphical display of select laboratory parameters over the course of the study will be provided.

Vital sign measurements and ECOG performance status will be listed for each subject at each visit. Descriptive statistics for the vital signs and ECOG performance status, both observed values and changes from baseline, will be summarized by treatment group.

10.8. Interim Analysis

One interim analysis to assess futility will be performed 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%. Based on the study assumptions, the interim analysis is projected to occur approximately 28 months after the first subject is randomized and at least 60% of subjects have been accrued. At the time of the interim analysis, based on blinded data, the death rate will be evaluated relative to the study assumptions and enrollment into the study may be increased to ensure that the required number of 330 deaths can be reached in approximately 60 months from the time of randomization of the first subject.

[redacted]

[redacted]

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition including AML relapse) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an IP should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of IP or until the last study visit, whichever period is longer. Adverse events and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. Please note that SPMs will be monitored as events of interest throughout the duration of the study including post treatment follow-up period and must be reported as SAEs regardless of the treatment arm the subject is in.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;

- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Second primary malignancies will be monitored as events of interest and must be reported as SAEs regardless of the treatment arm the subject is in (see Section 11.5).

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

11.2.2. Severity / Intensity

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the currently active minor version of Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3. Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (return to baseline), recovered with sequelae, or death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

11.4. Pregnancy

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 3 months of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form.

The female should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or

other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant while the male subject is on IP, or within 3 months of the male subject's last dose of IP, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Where applicable, the IP may need to be discontinued in the male subject but may be resumed later at the discretion of the Investigator and Medical Monitor.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

Development of SPMs will be monitored as events of interest throughout the duration of the study including the post treatment follow-up period and must be reported as SAEs regardless of the treatment arm the subject is in. This includes any SPM, regardless of causal relationship to IP (oral azacitidine or placebo), occurring at any time for the duration of the study, from the time of signing the ICD until death, lost to follow-up, withdrawal of consent for further data collection, or study closure. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF, ie, AE and SPM and subject's source documents. Documentation on the diagnosis of progression to AML and/or the SPM must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, X-rays, computed tomography [CT] scans, etc.).

The investigator is required to ensure that the data on these forms are accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent to 28 days after the last dose of IP or until the last study visit, whichever period is longer), and those made known to the investigator at anytime thereafter that are suspected of being related to IP. Serious AEs occurring prior to treatment but after informed consent will be collected.

The SAE report should provide a detailed description of the SAE and include a summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to oral azacitidine based on the Azacitidine IB.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the investigator of the following information (in Japan, Celgene KK shall notify the heads of the institutes in addition to the investigators):

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR).
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- In Japan, measures taken in foreign countries to ensure subject safety, study reports that indicate potential risk of cancer, etc, or biannual SAE report according to the local regulations.

Where required by local legislation, the investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form/Completion Guidelines or to the Pregnancy Report Form/Completion Guidelines.

12. DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the IP / treatment:

- Disease relapse

  Subjects will be discontinued from treatment when they meet the following criteria.

  – Appearance of > 15% blasts in the bone marrow or peripheral blood; and

  – The above occurrence should be attributed to relapse following CR/CRi, and not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy or myeloid growth factor administration).

- AE(s)
- Subject withdraws from active treatment but continues follow-up
- Subject becomes eligible (per Investigator) for allogeneic bone marrow or stem cell transplantation during treatment period
- Death
- Lost to follow up
- Protocol violation

Prior to discontinuing IP treatment for a subject assessed to have disease relapse, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

The reason for discontinuation will be recorded in the CRF and in the source documents.

All subjects discontinued from protocol prescribed treatment for any reason should undergo Treatment Discontinuation procedures including pregnancy test for FCBP. Additionally, all subjects discontinued from protocol prescribed treatment will be followed for a period of 28 days following the last dose of IP or until the date of the last study visit, whichever is later, for the collection of adverse events. Discontinued subjects will not be replaced.

During the follow-up period, all subjects should be followed every month for the first year and then every 3 months thereafter until death for collection of information on survival, AML relapse, monitoring for SPM and subsequent AML therapies, unless the subject has specifically withdrawn consent from further follow-up. Documentation such as laboratory or pathology reports, bone marrow and/or peripheral blood reports supporting the AML relapse will be requested and collected. The Investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow-up.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page).This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/CRO Medical Monitor, who will then contact you promptly.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued.

The Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject. However, the decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should be performed only by the Investigator through the IVRS by using an emergency unblinding personal identification number (PIN), and the Investigator should call IVRS for unblinded dose information.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC and any additional local authorities as appropriate, depending on local legislations for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

The sponsor may consider closing this trial when data supporting key endpoints and objectives of the study have been analyzed. In a case where there are subjects still being administered the investigational product, and it is the opinion of the investigator(s) that those subjects would continue to receive benefit from treatment, the sponsor may choose to initiate an open-label rollover study under a separate protocol to allow those subjects to continue receiving oral azacitidine. This would occur after their participation in this study, CC-486-AML-001, and after the unblinding of those remaining subjects.

The EP of the study will close once oral azacitidine becomes commercially available and reimbursed in the participating countries for the indications that the subjects are being treated such that the subject's access to oral azacitidine is neither interrupted nor discontinued.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the Investigator and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. At each monitoring visit, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and Good Clinical Practice.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g., FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

19. APPENDICES

Appendix A: 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 neoplasm

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: Swerdlow, SH, Campo, E, Harris, NL, Jaffe, ES, Pileri, SA, Stein, H, et al. editors. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: IARC Press; 2008; 109-139.

Appendix B: 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]

Appendix C: 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]

Appendix D: New York Heart Association Classification for Congestive Heart Failure

Functional Capacity
Class I. Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III. Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: [redacted]

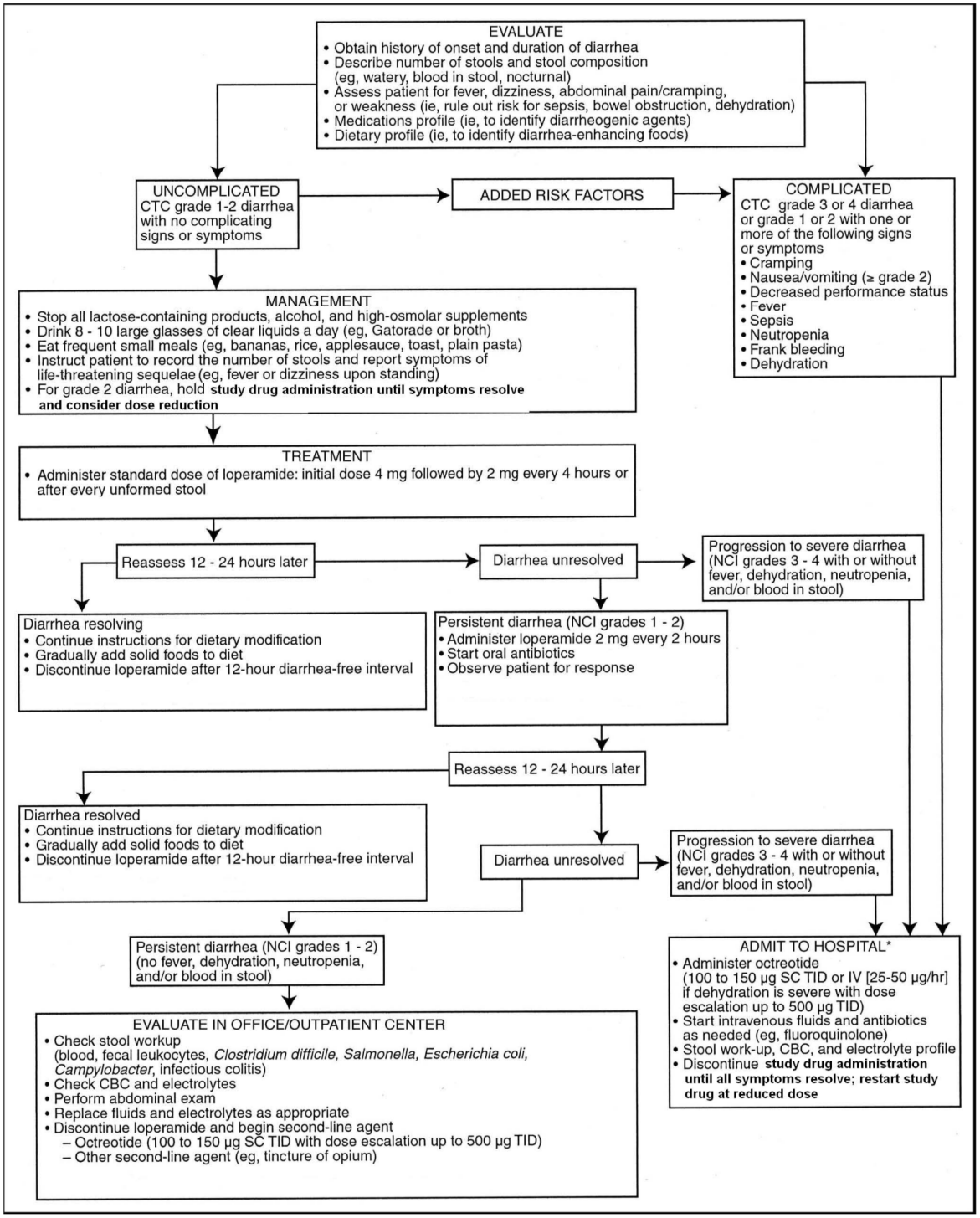
Appendix E: International Working Group AML Response Criteria

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]

Appendix I: Recommendations for Management of Treatment-Induced Diarrhea

The following published guidelines [redacted] were modified in order to be consistent with the clinical study protocol.



Appendix J: List of Abbreviations and Definitions of Terms

AE	Adverse event
ALT	Alanine transaminase (also known as SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate transaminase (also known as SGOT)
BSA	Body surface area
BSC	Best supportive care
BID	Twice a day
BUN	Blood urea nitrogen
CBC	Complete blood count
CC-486	Oral azacitidine
CCR	Conventional care regimen
CMML	Chronic myelomonocytic leukemia
CR	Complete remission
CRc	Complete cytogenetic remission
Cri	Complete remission with incomplete blood count recovery
CRF/eCRF	Case report form/electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EP	Extension Phase
EPO	Erythropoietin
EORTC	European Organization for Research and Treatment of Cancer
ESA	Erythropoiesis stimulating agent
FAB	French-American-British
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FACIT-Fatigue Scale	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related Quality-of-Life
IB	Investigator's Brochure
ICD	Informed Consent Document
INT-2	Intermediate-2
IP	Investigational Product

Appendix J: List of Abbreviations and Definitions of Terms (Continued)

IPSS	International Prognostic Scoring System
ITT	Intent to Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWG	International Working Group
LDH	Lactate dehydrogenase
KM	Kaplan-Meier
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCR	Marrow complete response
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Affairs
mRNA	Messenger-ribonucleic acid
miRNA	Micro-ribonucleic acid
mITT	Modified intent-to-treat
MRC	Medical Research Council
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	Overall survival
PFS	Progression-free survival
PR	Partial remission
pRBC	Packed red blood cell
QD	Once a day
QoL	Quality-of-life
RA	Refractory anemia
RAEB	Refractory anemia with excess blasts
RAEB-T	Refractory anemia with excess blasts in transformation
RARS	Refractory anemia with ringed sideroblasts
RBC	Red blood cell
RNA	Ribonucleic acid
RFS	Relapse-free survival
SAE	Serious adverse event
SC	Subcutaneous
SDev	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (also known as AST)
SGPT	Serum glutamic pyruvate transaminase (also known as ALT)
SOP	Standard operating procedure
SPM	Second primary malignancy
SRC	Synopsis Review Committee
SNP	Single nucleotide polymorphism
TEAE	Treatment-emergent adverse event

Appendix J: List of Abbreviations and Definitions of Terms (Continued)

TSA	Thrombopoiesis-stimulating agent
ULN	Upper Limit of Normal
US	United States
WBC	White blood cell
WHO	World Health Organization

Appendix K: Extension Phase

Subject Eligibility

At the Investigator's discretion and with approval of the sponsor, subjects meeting all of the following eligibility criteria are eligible to enter the extension phase:

1. All subjects randomized into the oral azacitidine or placebo arm and are continuing in either the Treatment Phase or Follow-up Phase of the CC-486-AML-001 study;
    - Subjects randomized to oral azacitidine treatment arm and continuing in the Treatment Phase demonstrating clinical benefit as assessed by the Investigator are eligible to receive oral azacitidine in the EP;
    - Subjects randomized into placebo arm of the study will not receive oral azacitidine in the EP, but will be followed for survival in the EP;
    - Subjects currently in the in the Follow-up Phase will continue to be followed for survival in the EP;
2. Subjects who have signed the informed consent for the EP of the study;
3. Subjects who do not meet any of the criteria for study discontinuation (see Section 12).

Treatment Assignment

Once the total number of events (n=330 deaths) required for a fully powered analysis of overall survival have occurred and the Amendment 2 of the protocol is approved at the respective sites, subjects will start the EP at the start of their next regularly scheduled dosing cycle for oral azacitidine and align Cycle 1 Day 1 with the Treatment Discontinuation visit for Protocol Amendment 1, so they occur on the same day. The dose and schedule for the first treatment cycle in the EP should be administered at the identical dose and schedule as the final treatment cycle in the Protocol Amendment 1. If a dose modification was required in the last cycle of Amendment 1, the first treatment cycle should be administered at the identical (modified) dose and/or schedule.

Cycles should be repeated every 28 days. Subjects should be monitored locally for hematology and chemistry testing, pregnancy testing for FCBP and dose limiting toxicities before the dosing of the next cycle. Dosage delay or reduction as described below may be necessary.

Management of Toxicities and Dose Modifications

Subjects should be monitored for toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0, as a guide for the grading of severity. If a certain level of toxicity is observed and considered by the investigator to be at least possibly related to treatment, IP dosing may be interrupted, delayed or modified. In all cases, the reason for dose modification must be recorded in the subject's medical record. If the subject discontinues the protocol-prescribed therapy because of an AE, this event must be reported in accordance with the procedures outlined in Section 8.2.5.

Oral azacitidine dose modifications due to nonhematological and hematological toxicities during oral azacitidine treatment should be managed as described in Section 8.2.5 for dose modification guidelines due to toxicity.

Dose and schedule adjustment in patients with AML relapse/progression will be performed as described in Section 8.2.6

Adverse Events

Adverse events (non-serious and serious) will continue to be collected in the EP AE CRF. Refer to Section 11 Adverse Events (AEs) for reporting requirements, responsibilities and procedures.

For subjects entering the EP, ongoing AEs at the time of the end of study visit from Protocol Amendment 1 should be left as ongoing and should not be recorded again in the EP AE CRF. Adverse events with an onset date equal to or after the EP informed consent date should be recorded in the AE CRF for Amendment 2. If a previously reported AE during Amendment 1 worsens during the EP, then the AE should be recorded as a new AE with a higher grade on the EP AE CRF. All subjects will be monitored for AEs for 28 days following the date of last dose of IP. SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (return to baseline), recovered with sequelae, or death (due to the SAE).

Concomitant Medications

All concomitant medications that are necessary for the subject's welfare may be given at the Investigator's discretion during the EP. However, treatment with any other investigational medication is not permitted. Refer to Section 9 for prohibited concomitant medications/therapy for subjects on oral azacitidine.

Survival Follow-up

All subjects participating in the EP will be followed for overall survival for an additional 12 months or more. During the survival follow up, subjects will be followed for survival every month for the duration of the survival follow-up, until death, withdrawal of consent for further follow-up, study termination, or until a subject is lost to follow-up. New anticancer therapies should be collected at the same time schedule.

Survival follow-up may be conducted via telephone contact with the subject, family, or the subject's treating physician or via record review (including public records, if admissible by law in the participating countries).

Recommended Monitoring of Subjects

1. Complete blood count with WBC differential and platelet count as needed, and at a minimum, prior to each dosing cycle.
2. For FCBP, pregnancy testing must be done prior to initiating new cycle
3. Bone marrow biopsy and aspirate as clinically indicated.
4. Additional tests or more frequent monitoring are at the Investigator's discretion based on the subject's clinical status.

Investigator's Responsibility

1. Complete Extension Phase Case Report Form pages.
2. Document all adverse events (serious and non-serious) on the adverse event log page of the Extension Phase Case Report Form as required by the protocol (Section 8.2.5).

3. Report serious adverse events and other immediately reportable events, as required by the protocol (see Section 11). A completed SAE form must be faxed to Celgene Drug Safety, as detailed in the Serious Adverse Event Report Form Completion Guidelines, immediately (ie, within 24 hours of the Investigator's knowledge of the event).
4. Report to the Sponsor about/of drug accountability.
5. Report to the Sponsor and complete the case report form page for extension phase termination when the subject completes, discontinues, or terminates treatment with oral azacitidine.
6. The subject should stop treatment with oral azacitidine if any of the following occur:
    a. Additional investigational treatment is started;
    b. Subject is no longer receiving clinical benefit, as per Investigator's discretion;
    c. Subject withdraws consent;
    d. A CTCAE toxicity Grade 3 or 4 that represents a worsening from baseline (prior to the first dose) persists for more than 21 days, despite the temporary interruption of oral azacitidine;
    e. A positive pregnancy test in a FCBP, at any time; or
    f. At the specific request of the Sponsor or its authorized representative.
4. The Investigator must be available for periodic monitoring visits and allow the Sponsor access to all medical records.
5. The Investigator will maintain source documents on the subject for all case report form data points, which include the following:
    a. Informed consent;
    b. Adverse events;
    c. Dosing information (date of administration, dose, number of tablets used, and lot number);
    d. Concomitant medications
    e. Termination date and reason.

Statistical Methods

Safety evaluation for the EP will include monitoring for adverse events and recording of concomitant medications. Although physical examinations, vital sign measurements and laboratory assessments will be performed in the EP, these assessments will not be captured in the CRF. However, clinically significant findings from these assessments which meet the definition of an adverse event (see Section 11) will be reported as adverse events. Adverse events will be summarized as per Protocol Section 11.3 on the subjects entering into the EP. Exposure to oral azacitidine as well as concomitant medications taken during the EP will also be summarized.

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, 09 November 2018, 03:41 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

– SUMMARY OF CHANGES –

AMENDMENT NO. 2.0

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

INVESTIGATIONAL PRODUCT (IP):	Oral Azacitidine (CC-486)
PROTOCOL NUMBER:	CC-486-AML-001
ORIGINAL DATE:	15 Aug 2012
AMENDMENT No. 1.0 DATE:	29 Dec 2015
AMENDMENT No. 2.0 DATE:	08 Nov 2018
EudraCT NUMBER:	2012-003457-28
IND NUMBER:	074618

Contact Information:

Name:	Ignazia La Torre, MD
Title:	[redacted]
Address:	[redacted]
	[redacted]
Phone:	[redacted]
E-mail:	[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

The primary purpose of this protocol amendment is to add an extension phase (EP) [redacted]

In addition, all subjects who were discontinued from the treatment phase (irrespective of randomization arm) and continuing in the Follow-up Phase, will be followed for survival for at least another 12 months, until death, withdrawal of consent, study closure or until the subject is lost to follow-up.

Revised Sections: Protocol Summary, Sections 4.1 and Appendix K

Minor changes included in this amendment are summarized below:

- Duration of the study and subject enrollment period was updated

  Revised Section: Protocol Summary and Section 4.1

- Revised language [redacted]

  Revised Sections: Protocol Summary

- Added language to the protocol that would define End of Trial or Closure of the Study. [redacted]

  Revised Sections: Section 4.1, Section 4.3, Section 14.8

- Revised language [redacted].

  Revised Sections: Table 1, Section 6.4, Section 6.9, Section 10.9.1

- Included a few minor editorial corrections and additions to Appendix J, List of Abbreviations and Definitions of Terms.

  Revised Section: Appendix J

- On recommendations from Health Regulatory Authorities, deleted language that indicated 'Adverse events such as disease progression, death related to disease progression (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the sponsor to regulatory authorities…'.

  Revised Section: Section 11.6

- Included an administrative change [redacted].

  Revised Section: Medical Monitor/Emergency Contact Information Page

- Included an administrative change [redacted]

  Revised Section: Celgene Therapeutic Area Head Signature Page

- A few minor editorial corrections were made globally.

  Revised Section: Global

– SUMMARY OF CHANGES –

AMENDMENT NO. 1.0

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

INVESTIGATIONAL PRODUCT (IP):	CC-486 (Oral Azacitidine)
PROTOCOL NUMBER:	CC-486-AML-001
ORIGINAL DATE:	15 Aug 2012
AMENDMENT No. 1.0 DATE:	29 Dec 2015
EudraCT NUMBER:	2012-003457-28
IND NUMBER:	074618

Contact Information:

Name:	Barry Skikne, MD, FACP; FCP (SA)
Title:	[redacted]
Address:	[redacted]
Phone:	[redacted]
E-mail:	[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}

Signature of Celgene Therapeutic Area Head **dd mmm yyyy**

[redacted]

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. **Modification of Inclusion Criterion #2 to allow patients with AML secondary to chronic myelomonocytic leukemia (CMML) into the study**

Revised Sections: Protocol Summary, Sections 4.1, 6.3, 7.1, 7.2, 7.3, 8.3, and 10.6.2.3

2. **Modification of Inclusion Criterion #4 to amend the amount of time required for subjects to be in complete remission (CR) or in complete remission with incomplete blood count recovery (CRi) from 3 months to 4 months (± 7 days).**

provided no delays occur because of adverse events, such as infections leading to [redacted]

Revised Sections: Global

3. **Reduction of the number of bone marrow collections and analyses for CR/CRi assessment**:

   [redacted]

   Revised Sections: Protocol Summary, 4.1, Figure 1 (footnote 2), Table 1 (footnote 17), Section 6.7

4. **Reduction in the number of clinical visits in a cycle beginning with Cycle 25:**

   [redacted]

   Revised Section: Table 1 heading (including footnote 30)

Minor changes included in this amendment are summarized below:

- Replaced the word "demonstrate" in the Primary Objective with "evaluate" [redacted]

  Revised Section: Protocol Summary and Section 2.1

- [redacted]

- Updated the number of sites participating in the clinical trial from 150 to 180.

  Revised Section: Protocol Summary, Sections 4.1, 7.1

- Revised language [redacted]

  Revised Section: Protocol Summary (deleted from Page 8) and Section 4.1 (deleted from Page 30)

- Provided clarification on HRQoL assessments and added the assessment of Physical Impairment Numeric Rating Scale, which had been omitted.

  Revised Sections: Protocol Summary, Table 1 (footnote 25), Sections 6.4, 6.9

- Added language [redacted]

  Revised Section: Section 1.2

- [redacted]

- Additional clarification provided regarding the timing of ECOG assessments.

  Revise Section: Table 1 (footnote 6)

- Corrected a typographical error in the study title.

  Revised Section: Title (Page 1)

- Corrected a typographical error to clarify that the Study Sponsor will review eligibility criteria prior to randomization.

  Revised Section: Section 6.3

- Clarification provided regarding the time that concomitant medications should be recorded.

  Revised Section: Sections 6.6.8, 9

- Removed a duplicate reference for guidance related to ≥ Grade 3 nausea and/or vomiting

  Revised Section: Table 2

- Added additional clarification for mid-cycle treatment schedule escalations.

  Revised Section: Section 8.2.6

- Corrected a typographical error for the spelling of pomalidomide.

  Revised Section: Section 9.2

- Added language to the protocol that would enable the implementation of a roll-over protocol.

  [redacted]

  Revised Sections: Protocol Summary, Sections 4.1, 4.3, 14.8

- Included a few minor editorial corrections and additions to Appendix J, List of Abbreviations and Definitions of Terms.

  Revised Sections: Appendix J

- Modified the wording concerning the involvement of the Medical Monitor in the unblinding and discontinuation of trial subjects. [redacted]

  Revised Section: Sections 8.9, 13.2

- Clarified the wording concerning the blast percentage cut-off for study discontinuation from ≥ 16% to > 15%.

  Revised Section: Global

- Implemented a revision to the protocol language [redacted]

  Revised Sections: Protocol Summary and Sections 4.1, 4.2

- Corrected a typographical error in Section 7.2 to replace "Adequate bone marrow function based on ANCs ≥ 0.5 x 10^9/L and platelet counts ≥ 20,000 x 10^9/L" with "Adequate bone marrow function based on ANCs ≥ 0.5 x 10^9/L and platelet counts ≥ 20 x 10^9/L."

  Revised Section: Section 7.2

- Revised language [redacted]

  Revised Section: Table 1 (footnote 17) and Section 6.1

- Provided guidance on handling of vomited doses of IP.

  Revised Section: Section 8.2.4

- Provided further guidance on the modification of doses and dosing schedule for toxicity and during AML relapse/progression.

  Revised Section: Sections 8.2.5, 8.2.6, and Table 2

- Corrected a typographical error [redacted]

  Revised Section: Section 11.5

- Updated References Section with 2 additional references [redacted]

  Revised Section: Section 18

- Revised Appendix G (EQ-5D Health Questionnaires) [redacted]

  Revised Section: Appendix G

- Included an administrative change [redacted]

  Revised Section: Celgene Therapeutic Area Head Signature Page

- A few minor editorial corrections were made globally.

  Revised Section: Global