Official Title of Study:

A Phase 2, 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 Japanese Subjects with Acute Myeloid Leukemia in Complete Remission

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CLINICAL PROTOCOL CA055005

A Phase 2, 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 Japanese Subjects with Acute Myeloid Leukemia in Complete Remission

Brief Title:

A Study of Oral Azacitidine or Placebo with Best Supportive Care as Maintenance Therapy in Japanese Subjects with Acute Myeloid Leukemia in Complete Remission

Protocol Amendment 02

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 02	27-Jun-2023	The CA055-005 study amendment 02 reflects the recent changes of clinical practice in the treatment of newly diagnosed AML, that have impacted study feasibility and enrollment. The changes of amendment 02 includes revisions to the schedule of activities, risk assessment, exploratory objectives and endpoints, number of participants, intensive PK samples, and statistical considerations.
Administrative Letter 02	24-Oct-2022	Corrected misspelling
Administrative Letter 01	10-Oct-2022	Updated study personnel information
Protocol Amendment 01	25-July-2022	Amendment 01for CA055055 includes addition of an Eastern Cooperative Oncology Group (ECOG) performance status as a new inclusion criterion. Additionally, updates are made to clarify the assessments to be performed at appropriate time points, improve alignment across protocol sections and establish consistency, and update contact information.
Original Protocol	21-Aug-2021	Not applicable

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OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

The CA055005 study amendment 02 reflects the recent changes of clinical practice in the treatment of newly diagnosed AML with improved access to allogeneic transplantation (including older patients), the approval of non-intensive induction regimen such as azacitidine venetoclax, and the use of more extensive consolidation regimens (3 and more cycles). This has impacted study feasibility and enrollment. The changes of amendment 02 include revisions to the number of participants, schedule of activities, risk assessment, exploratory objectives, references to number of intensive PK sampling, and statistical considerations. Additionally, the changes which were previously updated by the administrative letters, have been incorporated into this amendment.

Other revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Protocol Summary	Updated to reflect changes in the body of the protocol.	For consistency across the protocol.
Table 2-1: Screening Procedural Outline Table 2-2: On treatment Procedural Outline Table 2-3: End-of-treatment and Follow-up Procedural Outline Table 4-1: Exploratory Objectives and Endpoints 9.7 Biomarkers Table 9.7-1: Biomarker	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology testing and exploratory evaluation removed.	To align with the updated SARS-CoV-2 protocol guidance document.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Sampling Schedule (All Participants) 10.4.4 Exploratory Endpoint(s)		
Table 3.3.1-1: Risk Assessment	Hypotheses for sample size calculation removed from Study Procedures, Study Design section.	To reflect change of statistical analysis plan.
Table 3.3.1-1: Risk Assessment	Risk of small sample size and mitigation strategy were added.	Due to change in the number of participants.
5.1Overall Design Figure 5.1-1: Study Design Schema 5.2 Number of Participants 10.2 Sample Size Determination	Number of participants in total was changed from 66 to 15. And accordingly, the number of participants receiving CC-486 and the number of participants receiving placebo has changed.	Number of participants was modified based on change of enrollment plan.
Section 9.5 Pharmacokinetics	References to the number of participants undergoing intensive PK sampling were removed.	Due to change in the number of participants.
10.1 Statistical Hypotheses 10.4.2 Primary Endpoint(s)	Hypothesis testing removed and a Cox proportional hazards model was added.	To reflect change of statistical analysis plan.
10.1 Statistical Hypotheses	Timing of analysis of the primary endpoint was added.	To reflect change of statistical analysis plan.
10.2 Sample Size Determination	The threshold for the median RFS for placebo and expected median RFS for CC-486 were removed.	To reflect change of statistical analysis plan.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	The hazard ratio based on the changed number of participants was added.	
All Description	Minor edits and clarifications were made.	Minor, therefore have not been summarized.

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1 PROTOCOL SUMMARY

Protocol Title:

A Phase 2, 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 Japanese Subjects with Acute Myeloid Leukemia in Complete Remission

Brief Title:

A study of Oral Azacitidine or Placebo with Best Supportive Care as Maintenance Therapy in Japanese Subjects with Acute Myeloid Leukemia in Complete Remission

Rationale:

The standard treatment modality for acute myeloid leukemia (AML) is chemotherapy globally as well as in Japan. The therapeutic approaches are usually divided into two phases: induction of remission and post-remission (consolidation) therapy. A common induction regimen consists of cytarabine 100 mg/m2/day for 7 days combined with daunorubicin 60 to 90 mg/m2/day for 3 days, often referred to as the "7+3 protocol." For post-remission chemotherapy, the same chemotherapy agent(s) used for remission induction is often repeated for one or more cycles, referred to as consolidation chemotherapy. When several courses of consolidation are given, despite achieving complete remission (CR), approximately 50% of younger (< 60 years old) and 80% to 90% of older patients will relapse, and most of these patients will die due to AML, with median survival from 3 to 12 months after relapse. For patients with relapsed AML, the duration of first CR is strongly correlated with subsequent outcomes, with longer duration of first CR associated with better survival. Up to the present time, there has not been any successful maintenance therapy that has led to a benefit in prolonging survival for patients achieving CR after intensive chemotherapy. Therefore, an unmet medical need exists for maintaining a deeper level of remission over a longer duration in patients who achieve remission. Effective maintenance therapy for patients who attain remission with intensive chemotherapy may play a role in preventing relapse and prolonging overall survival (OS), especially in those ineligible for allogeneic hematopoietic stem cell transplantation.

CC-486 (oral azacitidine) was confirmed to show statistically significant prolongation of OS and relapse-free survival (RFS) in the maintenance setting in patients ≥ 55 years of age with AML, and in CR or complete remission with incomplete blood count recovery (CRi) after conventional induction chemotherapy with or without consolidation chemotherapy in Study CC-486-AML-001. CC-486 was already approved for the treatment of AML in the United States in September 2020, in Canada in January 2021, and in the European Union in June 2021. CC-486 is recommended for the treatment of AML patients in complete remission as maintenance therapy regardless of age (< 60 years or ≥ 60 years) per the National Comprehensive Cancer Network clinical practice guideline (Category 2B).

CA055005 is a bridging study to provide clinical data that will allow extrapolation of the CC-486-AML-001 study data to Japan. This study is designed as a 2:1 randomization of CC-486 or placebo to assess the efficacy and safety of maintenance treatment with oral azacitidine in a cohort of

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Japanese participants ≥ 55 years of age with AML and in CR/CRi after conventional induction chemotherapy with or without consolidation chemotherapy. The primary endpoint of RFS and secondary endpoints of OS, safety, pharmacokinetics (PK), and health-related quality of life (HRQoR) will be evaluated and allow for a comprehensive investigation of the efficacy, exposure/safety, and HRQoL appropriateness of clinical recommended dose for the Japanese population in comparison with the data from the Study CC-486-AML-001.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of CC-486 as maintenance therapy by using RFS in Japanese participants with ≥ 55 years with AML, who have achieved first CR or CRi after induction with intensive chemotherapy with or without consolidation chemotherapy.	• RFS
Secondary	
• To determine the effect of CC-486 as maintenance therapy on OS, time to relapse from CR/CRi, and time to discontinuation from treatment • To determine safety and tolerability • To determine PK • To determine the effect of CC-486 on HRQoL	• OS • 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) • PK parameters • Participant-reported outcomes utilizing the FACIT-Fatigue Scale and the EQ-5D-5L

Abbreviations: AE, adverse event; AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete blood count recovery; DNA, deoxyribonucleic acid; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; OS, overall survival; PK, pharmacokinetic(s); RFS, relapse-free survival.

Overall Design:

This is a multicenter, placebo-controlled, Phase 2 study with a double-blind, randomized, 2:1 group design in Japanese participants 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.

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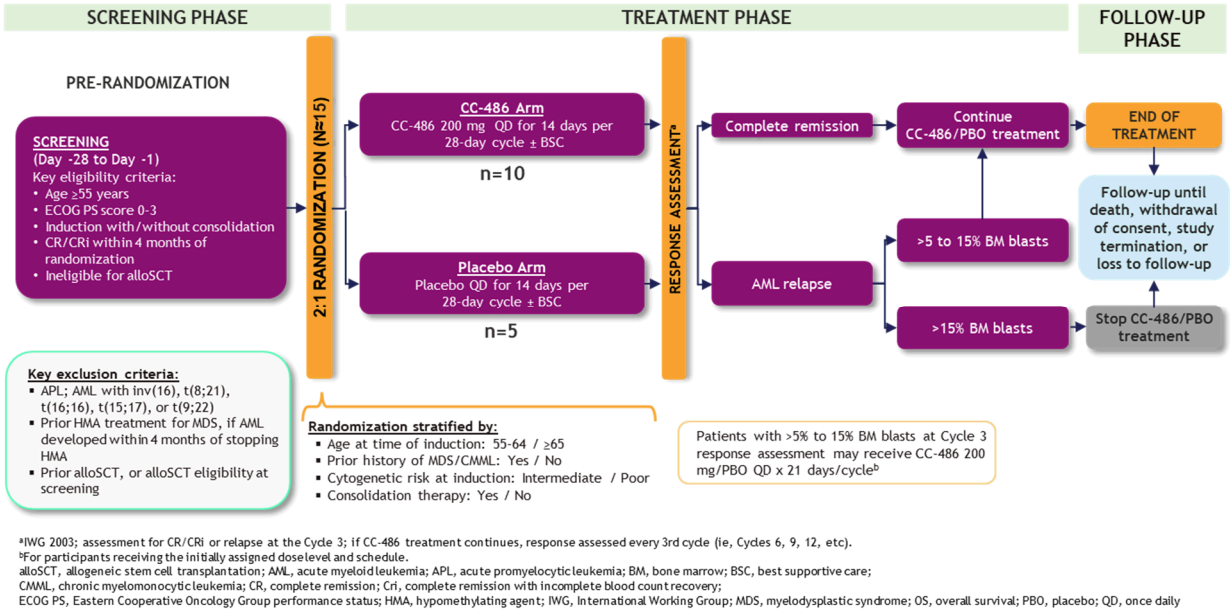

[a]IWG 2003; assessment for CR/CRi or relapse at the Cycle 3; if CC-486 treatment continues, response assessed every 3rd cycle (ie, Cycles 6, 9, 12, etc).
[b]For participants receiving the initially assigned dose level and schedule.
alloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BM, bone marrow; BSC, best supportive care; CMML, chronic myelomonocytic leukemia; CR, complete remission; Cri, complete remission with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agent; IWG, International Working Group; MDS, myelodysplastic syndrome; OS, overall survival; PBO, placebo; QD, once daily

Number of Participants:

Approximately 15 participants will be randomized 2:1 to receive CC-486 or placebo.

Study Population:

Key inclusion criteria

- Participant must be ≥ 55 years of age inclusive at the time of signing the informed consent
- Newly diagnosed, histologically confirmed de novo AML or AML secondary to prior MDS or CMML.
- Should have undergone induction therapy with intensive chemotherapy with or without consolidation therapy as recommended in appropriate guideline(s) or equivalent regimen according to institutional standard: having achieved first CR/CRi status within 4 months (± 7 days) prior to randomization.

Key exclusion criteria

- Suspected or proven acute promyelocytic leukemia (FAB M3); or AML with previous hematologic disorder such as chronic myeloid leukemia or myeloproliferative neoplasms, excluding MDS and CMML.
- 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.
- Prior bone marrow or stem cell transplantation.
- Candidate for allogeneic bone marrow or stem cell transplant at screening.
- Have achieved CR/CRi following therapy with hypomethylating agents
- Received therapy with hypomethylating agents for MDS and went on to develop AML within four months of discontinuing the therapy with hypomethylating agents.

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Intervention Groups and Duration:

Total duration of study participation for each participant: screening phase for 4 weeks, treatment phase until AML relapse, and follow-up phase until death, withdrawal of consent, study termination, or loss to follow-up.

Dose regimen: 200 mg once daily of CC-486 or placebo will be taken for the first 14 days of each 28-day treatment cycle.

Dose modification for toxicity and dose/schedule adjustment with AML relapse are allowed.

Study Intervention:

Study Intervention for CA055005		
Medication	**Potency**	**IP/Non-IP/AxMP**
CC-486	150mg/200mg	IP
Placebo	150mg/200mg	IP

Abbreviations: AxMP, auxiliary medicinal product; IP, Investigational Product.

Statistical Methods:

The primary efficacy analysis will be conducted for the Intent-to-Treat Population and will compare the RFS distributions between the two treatment groups. A Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI for CC-486 relative to placebo. The RFS curves will be estimated using Kaplan-Meier methods.

Data Monitoring Committee: No

A Data Monitoring Committee or other review committee will not be used in the study.

Other Committee: No

Other review committee will not be used in the study.

Brief Summary:

CA055-005 is designed as a 2:1 randomization of CC-486 or placebo to assess the efficacy and safety of maintenance treatment with oral azacitidine in a cohort of Japanese participants ≥ 55 years with AML, and in CR/CRi after intensive induction chemotherapy with or without consolidation chemotherapy. The primary endpoint of RFS and the secondary endpoints of OS, safety, PK, and HRQoL will be evaluated and allow for a comprehensive investigation of efficacy, exposure/safety, and appropriateness of the clinical recommended dose for the Japanese population in comparison with the data from Study CC-486-AML-001.

Study Duration: 3 years

Study Intervention Duration: Until AML relapse in each participant.

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Study Visit Frequency: On Days 1, 8, 15 and 22 in Cycles 1 and 2, Days 1 and 15 in Cycles 3 through 24, and Day 1 in Cycle 25 and beyond.

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2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1 (Screening Procedural Outline), Table 2-2 (On Treatment Procedural Outline), and Table 2-3 (Follow-up Procedural Outline).

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Table 2-1: Screening Procedural Outline (CA055005)

Procedure	Screening (Day -28 to -1)[a]	Randomization (Day -3 to Day 1)	Notes
Eligibility Assessments			
Informed Consent	X		A participant is considered enrolled only when a protocol-specific informed consent is signed. Must be obtained prior to performing any screening procedures.
Inclusion/Exclusion Criteria	X		
Demographics and Medical History	X		All medical history relevant to disease under study
AML Diagnosis History	X		Documentation of AML diagnosis will be assessed locally from bone marrow aspirate and/or biopsy sample slides
Transplant Eligibility	X		Including reasons ineligible for transplant
Documentation of Induction ± Consolidation Therapies	X		Including cytogenetic risk category information at time of induction therapy
CR/CRi Status Confirmation	X		
Safety Assessments			
Physical Examination	X		Includes height and weight.
Vital Signs	X		Includes body temperature, blood pressure, heart rate, and respiratory rate.
ECOG Performance Status	X	X	See Appendix 5. Can be performed at randomization or Cycle 1 Day 1.
Prior Medications	X		Includes any prior chemotherapy, cytotoxic therapy, radiation therapy, and all medications used for the 4-week period prior to Cycle 1 Day 1.
12-Lead ECG	X		Electrocardiogram required during screening period and whenever clinically indicated. This is collected locally. For participants with an abnormal ECG, a cardiac consultation should be obtained as deemed necessary by the treating physician.
Chest X-ray	X		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. Chest x-ray is collected locally.

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Table 2-1: Screening Procedural Outline (CA055005)

Procedure	Screening (Day -28 to -1)[a]	Randomization (Day -3 to Day 1)	Notes
Adverse Event Reporting			
Monitor for Serious Adverse Events	X		All SAEs must be collected from the date of participant's written consent until 28 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Monitor for Non-Serious Adverse Events	X		All non-serious AEs must be collected from the date of participant's written consent until 28 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Laboratory Tests			See Section 9.4.4
Hematology	X		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 participant, local laboratory tests may be used. In addition to the local laboratory sample, a second sample should always be sent to the central laboratory.
Unstained Peripheral Blood Smear	X		Whenever a hematology sample is collected for a complete blood count, unstained peripheral blood smears 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	X		Includes serum chemistry laboratory tests (sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, 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 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 participant,

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Table 2-1: Screening Procedural Outline (CA055005)

Procedure	Screening (Day -28 to -1)[a]	Randomization (Day -3 to Day 1)	Notes
			local laboratory tests may be used. In addition to the local laboratory sample, a second sample should be sent to the central laboratory.
Coagulation	X		Coagulation testing is conducted at screening and whenever clinically indicated during the treatment phase.
Urinalysis	X		A standard urinalysis (including microscopic analysis if indicated) is required at screening and whenever clinically indicated during the treatment phase.
Pregnancy Test (WOCBP only)	X		A medically supervised serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained in female participants of childbearing potential at Screening (within 24 hours prior to starting study therapy).
Viral Serology	X		HBsAg, hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis C antibody, HIV antibody and if applicable HBV viral DNA and HCV viral RNA testing by PCR. For participants with HBV carrier or history of HBV infection (HBsAg negative and anti-HBs positive and/or anti-HBc positive), signs and symptoms of HBV reactivation should be continuously monitored during treatment with appropriate measures including liver function test and HBV marker as per the "Guidelines for Handling Hepatitis B Associated with Immunosuppression/Chemotherapy".[1]
Biomarker Assessments			See Table 9.7-1 for sampling schedule.
Biomarker Blood and Bone Marrow Sampling	X		Blood and bone marrow samples for biomarker assessment are mandatory and participant must consent to the collection of these samples.
Pharmacogenomic Blood Sampling	X		Peripheral blood sampling for pharmacogenomic analysis is mandatory and participant 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.
Efficacy Assessments			
Bone Marrow Aspirate	X		A bone marrow aspirate or biopsy (if adequate aspirate is not attainable) should ideally be collected at screening, no earlier than 14 days prior to Cycle 1 Day 1. The screening bone marrow aspirate and biopsy are required to be repeated even if

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Table 2-1: Screening Procedural Outline (CA055005)

Procedure	Screening (Day -28 to -1)[a]	Randomization (Day -3 to Day 1)	Notes
			a bone marrow aspirate and biopsy were 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.
Bone Marrow Biopsy	X		Bone marrow biopsies may be needed to assess bone marrow status.
Cytogenetic Testing	X		Bone marrow aspirate sample tube for cytogenetic testing/chromosome analysis to be obtained at Screening for evaluation by the central laboratory to obtain karyotype. A minimum of 16 analyzable metaphases for standard banding cytogenetic analysis is recommended at Screening.
Peripheral Blood Smear	X		Whenever bone marrow aspirate (or biopsy) slides are sent to the central reviewer, an unstained peripheral blood smear slide should also be submitted.
Study Intervention			
Randomization		X	Randomization should occur within 3 days of Cycle 1 Day 1.

Abbreviations: ALT, alanine aminotransferase; AML, acute myeloid leukemia; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, complete remission; CRi, complete remission with incomplete blood count recovery; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RNA, ribonucleic acid; PCR, polymerase chain reaction; SAE, serious adverse reaction; WBC, white blood cell; WOCBP, women of childbearing potential.

[a] Results obtained on Cycle 1 Day 1 just prior to the first dose will serve as the Baseline values. If not available, the most recent screening results prior to Cycle 1 Day 1 will be considered the Baseline values. Participants 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.

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Table 2-2: On-treatment Procedural Outline (CA055005)

Procedure	During Treatment Cycle 1 Day1 (1 Cycle = 4 Weeks)	During Treatment Cycle 1 Days 8, 15, and 22 (± 3 Days)	During Treatment Cycle 2 Day 1 (± 3 Days)	During Treatment Cycle 2 Days 8, 15, and 22 (± 3 days)	During Treatment Cycle 3 and beyond Day 1 (± 3 Days)	During Treatment Cycle 3 and beyond Day 15[a] (± 3 Days)	Notes
Safety Assessments							
Physical Examination	X		X		X		Includes weight.
ECOG Performance Status	X		X		X		
Vital Signs	X		X		X		Includes body temperature, blood pressure, heart rate, and respiratory rate.
Concomitant Medications, Therapy, and Procedures	X	X	X	X	X	X	All concomitant over-the-counter medications; prescription medications, including anti-infectives for prophylaxis and/or treatment of an infection; and non-live COVID-19 vaccines received 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.

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Table 2-2: On-treatment Procedural Outline (CA055005)

Procedure	During Treatment Cycle 1 Day1 (1 Cycle = 4 Weeks)	During Treatment Cycle 1 Days 8, 15, and 22 (± 3 Days)	During Treatment Cycle 2 Day 1 (± 3 Days)	During Treatment Cycle 2 Days 8, 15, and 22 (± 3 days)	During Treatment Cycle 3 and beyond Day 1 (± 3 Days)	During Treatment Cycle 3 and beyond Day 15[a] (± 3 Days)	Notes
Adverse Event Reporting							
Monitor for Serious Adverse Events	X	X	X	X	X	X	All SAEs must be collected from the date of participant's written consent until 28 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Monitor for Non-Serious Adverse Events	X	X	X	X	X	X	All non-serious AEs must be collected from the date of participant's written consent until 28 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Laboratory Tests							See Section 9.4.4.
Hematology	X	X	X	X	X	X	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

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Table 2-2: On-treatment Procedural Outline (CA055005)

Procedure	During Treatment Cycle 1 Day1 (1 Cycle = 4 Weeks)	During Treatment Cycle 1 Days 8, 15, and 22 (± 3 Days)	During Treatment Cycle 2 Day 1 (± 3 Days)	During Treatment Cycle 2 Days 8, 15, and 22 (± 3 days)	During Treatment Cycle 3 and beyond Day 1 (± 3 Days)	During Treatment Cycle 3 and beyond Day 15[a] (± 3 Days)	Notes
							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 test results are needed to acutely manage the participant, local laboratory tests may be used. In addition to the local laboratory sample, a second sample should always be sent to the central laboratory.
Unstained Peripheral Blood Smear	X	X	X	X	X	X	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	X		X		X		Includes serum chemistry laboratory tests (sodium,

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Table 2-2: On-treatment Procedural Outline (CA055005)

Procedure	During Treatment Cycle 1 Day1 (1 Cycle = 4 Weeks)	During Treatment Cycle 1 Days 8, 15, and 22 (± 3 Days)	During Treatment Cycle 2 Day 1 (± 3 Days)	During Treatment Cycle 2 Days 8, 15, and 22 (± 3 days)	During Treatment Cycle 3 and beyond Day 1 (± 3 Days)	During Treatment Cycle 3 and beyond Day 15[a] (± 3 Days)	Notes
							potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, 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 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 test results are needed to acutely manage the participant, local laboratory tests may be used. In addition to the local laboratory sample, a second sample should be sent to the central laboratory.

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Table 2-2: On-treatment Procedural Outline (CA055005)

Procedure	During Treatment Cycle 1 Day1 (1 Cycle = 4 Weeks)	During Treatment Cycle 1 Days 8, 15, and 22 (± 3 Days)	During Treatment Cycle 2 Day 1 (± 3 Days)	During Treatment Cycle 2 Days 8, 15, and 22 (± 3 days)	During Treatment Cycle 3 and beyond Day 1 (± 3 Days)	During Treatment Cycle 3 and beyond Day 15[a] (± 3 Days)	Notes
Pregnancy Test (WOCBP only)	X		X		X		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). If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from study participation if the serum pregnancy result is positive.
Pharmacokinetic Assessments							
Pharmacokinetics	X	X	X		X		Refer to pharmacokinetics collection table in Section 9.5 for timing of collections
Biomarker Assessments							
Biomarker Blood and Bone Marrow Sampling (from the same sample taken for central review; additional consent required)	See Section 9.7						Refer to biomarker collection table in Section 9.7 for timing of collections. Blood and bone marrow samples for biomarker assessment are mandatory and participant must consent to the collection of these samples. Samples should be

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Table 2-2: On-treatment Procedural Outline (CA055005)

Procedure	During Treatment Cycle 1 Day1 (1 Cycle = 4 Weeks)	During Treatment Cycle 1 Days 8, 15, and 22 (± 3 Days)	During Treatment Cycle 2 Day 1 (± 3 Days)	During Treatment Cycle 2 Days 8, 15, and 22 (± 3 days)	During Treatment Cycle 3 and beyond Day 1 (± 3 Days)	During Treatment Cycle 3 and beyond Day 15[a] (± 3 Days)	Notes
							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.
Pharmacogenomic Blood Sampling	See Section 9.7						Peripheral blood sampling for pharmacogenomic analysis is mandatory and participant 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.
Efficacy Assessments							
Bone Marrow Aspirate					X		Bone marrow aspirate must be collected on Day 1 (± 7 days) of Cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, and 36, 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 will be

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Table 2-2: On-treatment Procedural Outline (CA055005)

Procedure	During Treatment Cycle 1 Day1 (1 Cycle = 4 Weeks)	During Treatment Cycle 1 Days 8, 15, and 22 (± 3 Days)	During Treatment Cycle 2 Day 1 (± 3 Days)	During Treatment Cycle 2 Days 8, 15, and 22 (± 3 days)	During Treatment Cycle 3 and beyond Day 1 (± 3 Days)	During Treatment Cycle 3 and beyond Day 15[a] (± 3 Days)	Notes
							performed only if clinically indicated.
Bone Marrow Biopsy					X		Bone marrow biopsy may be needed to assess bone marrow status if an adequate bone marrow aspirate cannot be attained.
Cytogenetic Testing					X		Bone marrow aspirate sample tube for cytogenetic testing/chromosome analysis to be obtained for evaluation by central laboratory to obtain karyotype. During the study, repeat of bone marrow cytogenetic testing is to be completed whenever a bone marrow aspirate is obtained.
Peripheral Blood Smear					X		Whenever bone marrow aspirate (or biopsy) slides are sent to the central reviewer, a peripheral blood smear slide should also be submitted.
IWG Response Assessment					X		International Working Group (IWG) response assessment will be done at Cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, and 36. After Cycle 36, response assessment for disease relapse will be

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Table 2-2: On-treatment Procedural Outline (CA055005)

Procedure	During Treatment Cycle 1 Day1 (1 Cycle = 4 Weeks)	During Treatment Cycle 1 Days 8, 15, and 22 (± 3 Days)	During Treatment Cycle 2 Day 1 (± 3 Days)	During Treatment Cycle 2 Days 8, 15, and 22 (± 3 days)	During Treatment Cycle 3 and beyond Day 1 (± 3 Days)	During Treatment Cycle 3 and beyond Day 15[a] (± 3 Days)	Notes
							performed only if clinically indicated. Participants should be assessed for CR/CRi status maintenance, relapse after CR/CRi, or disease relapse.
Health Outcomes Assessments							
FACIT-Fatigue Scale and EQ-5D-5L	X		X		X		Each assessment should be completed at the start of the clinic visit prior to dosing and other study assessments. See Section 9.1.2.
Study Intervention							
Dispense/Administer	X		X		X		IP is scheduled to be taken for 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. Participants with ≥5% to ≤15% blasts in the bone marrow or peripheral blood response assessment may receive 200mg of IP for the first 21 days per cycle.
Provide/Collect Medication Diary	X		X		X		

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Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; COVID-19, coronavirus disease 2019; CR, complete remission; CRF, case report form; CRi, complete remission with incomplete blood count recovery; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; IgG, immunoglobulin G; IgM, immunoglobulin M; IP, Investigational Product; IWG, International Working Group; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; SAE, serious adverse event; WBC, white blood cell; WOCBP, women of childbearing potential.

[a] Beginning with the Cycle 25 Day 15 visit, assessments are optional and will occur only if clinically indicated at the discretion of the Investigator.

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Table 2-3: End-of-treatment and Follow-up Procedural Outline (CA055005)

Procedure	End of Treatment /Early Termination	Follow-up	Notes
Safety Assessments			
Physical Examination	X		Includes weight.
Vital Signs	X		Includes body temperature, blood pressure, heart rate, and respiratory rate.
Concomitant Medications, Therapy, and Procedures	X	X	All concomitant over-the-counter medications; prescription medications, including anti-infectives for prophylaxis and/or treatment of an infection; and non-live COVID-19 vaccines received 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.
Monitor for Serious Adverse Events Assessment	X	X	All SAEs must be collected from the date of participant's written consent until 28 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Monitor for Non-Serious Adverse Events	X	X	All non-serious AEs must be collected from the date of participant's written consent until 28 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Laboratory Tests			See Section 9.4.4.
Hematology	X		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 participant, local laboratory tests may be used. In addition to the local laboratory sample, a second sample should always be sent to the central laboratory.
Unstained Peripheral Blood Smear	X		Whenever a hematology sample is collected for a complete blood count, unstained peripheral blood smears should be prepared and sent to the central laboratory. This

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Table 2-3: End-of-treatment and Follow-up Procedural Outline (CA055005)

Procedure	End of Treatment /Early Termination	Follow-up	Notes
			unstained peripheral blood smear will be used to assess a manual blood count differential.
Serum Chemistry	X		Includes serum chemistry laboratory tests (sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, 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 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 test results are needed to acutely manage the participant, local laboratory tests may be used. In addition to the local laboratory sample, a second sample should be sent to the central laboratory.
Pregnancy Test (WOCBP only)	X		A serum or urine pregnancy test (per Investigator's discretion) is to be done at the EOT visit. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from study participation if the serum pregnancy result is positive.
Biomarker Assessments			
Biomarker Blood and Bone Marrow Sampling (from the same sample taken for central review; additional consent required)	X		Refer to biomarker collection table in Section 9.7 for timing of collections. Blood and bone marrow samples for biomarker assessment are mandatory and participant 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.
Pharmacogenomic Blood Sampling	X		Peripheral blood sampling for pharmacogenomic analysis is mandatory and participant 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.

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Table 2-3: End-of-treatment and Follow-up Procedural Outline (CA055005)

Procedure	End of Treatment /Early Termination	Follow-up	Notes
Efficacy Assessments			
Bone Marrow Aspirate	X		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 to 4 weeks later to confirm disease relapse unless the blast count was > 50% in the marrow or peripheral blood.
Bone Marrow Biopsy	X		Bone marrow biopsy may be needed to assess bone marrow status if an adequate bone marrow aspirate cannot be attained.
Cytogenetic Testing	X		Bone marrow aspirate sample tube for cytogenetic testing/chromosome analysis to be obtained for evaluation by central laboratory to obtain karyotype.
Peripheral Blood Smear	X		Whenever bone marrow aspirate (or biopsy) slides are sent to the central reviewer, a peripheral blood smear slide should also be submitted.
IWG Response Assessment	X		Participants should be assessed for CR/CRi status maintenance, relapse after CR/CRi, or disease relapse.
Follow-up AML Relapse		X	All discontinued participants, regardless of reason for discontinuation, should be followed for AML relapse every 4 weeks (± 3 days) for the first year and then every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent from further follow-up, or end of study. Documentation such as laboratory or pathology reports, bone marrow reports, and/or peripheral blood reports supporting the AML relapse should be requested and collected.
Follow-up AML Therapies		X	All discontinued participants, regardless of reason for discontinuation, should be followed for AML therapies every 4 weeks (± 3 days) for the first year and then every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent from further follow-up, or end of study.

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Table 2-3: End-of-treatment and Follow-up Procedural Outline (CA055005)

Procedure	End of Treatment /Early Termination	Follow-up	Notes
Survival Follow-up		X	All discontinued participants, regardless of reason for discontinuation, should be followed for survival every 4 weeks (± 3 days) for the first year and then every 12 weeks (± 14 days) until death, lost to follow-up, withdrawal of consent from further follow-up, or the end of the study. The survival follow-up can be performed via a telephone interview.
Health Outcomes Assessments			
FACIT-Fatigue Scale and EQ-5D-5L	X		Each assessment should be completed at the start of the clinic visit prior to dosing and other study assessments. See Section 9.1.2.

Abbreviations: ALT, alanine aminotransferase; AML, acute myeloid leukemia; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; CR, complete remission; CRF, case report form; CRi, complete remission with incomplete blood count recovery; EOT, end of treatment; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; IgG, immunoglobulin G; IgM, immunoglobulin M; IP, Investigational Product; IWG, International Working Group; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; SAE, serious adverse event; WBC, white blood cell; WOCBP, women of childbearing potential.

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3 INTRODUCTION

This is a Phase 2, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of CC-486 plus best supportive care versus best supportive care as maintenance therapy in Japanese participants with acute myeloid leukemia (AML) in complete remission. The primary objective of the study is to evaluate whether maintenance therapy with CC-486 improves relapse-free survival (RFS) compared with placebo in Japanese participants ≥ 55 years with AML, 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. Participants will be randomized 2:1 to receive 200 mg CC-486 once daily (QD) or placebo for the first 14 days of each 28-day treatment cycle.

A detailed description of the chemistry, pharmacology, efficacy, and safety of CC-486 is provided in the Investigator's Brochure (IB).

3.1 Study Rationale

The standard treatment modality for acute myeloid leukemia (AML) is chemotherapy globally as well as in Japan. The therapeutic approaches are usually divided into two phases: induction of remission and post-remission (consolidation) therapy. A common induction regimen consists of cytarabine 100 mg/m^2/day for 7 days combined with daunorubicin 60 to 90 mg/m^2/day for 3 days, often referred to as the "7+3 protocol." For post-remission chemotherapy, the same chemotherapy agent used for remission induction is often repeated for one or more cycles, referred to as consolidation chemotherapy. When several courses of consolidation are given, despite achieving complete remission (CR), approximately 50% of younger (< 60 years) and 80% to 90% of older (≥ 65 years) patients will relapse; most of these patients will die due to AML, with median survival from 3 to 12 months after relapse. For patients with relapsed AML, the duration of first CR is strongly correlated with subsequent outcomes, with longer duration of first CR associated with better survival. Therefore, an unmet medical need exists for maintaining a deeper level of remission over a longer duration in patients who achieve remission. Effective maintenance therapy for patients who attain remission with intensive chemotherapy may play a role in preventing relapse and prolonging overall survival (OS), especially in those ineligible for allogeneic hematopoietic stem cell transplantation (HSCT).

CC-486 was confirmed to show statistically significant prolongation of OS and relapse-free survival (RFS) in the maintenance setting in patients ≥ 55 years with AML and in CR or complete remission with incomplete blood count recovery (CRi) after conventional induction chemotherapy with or without consolidation chemotherapy in Study CC-486-AML-001. CC-486 was already approved for the treatment of AML in the United States (US) in September 2020, in Canada in January 2021, and the European Union in June 2021. CC-486 is recommended for as maintenance therapy for patients with AML in complete remission, regardless of age (<60 or ≥ 60 years), in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline (Category 2B).[2]

CA055-005 is a bridging study to provide clinical data that will allow extrapolation of the CC-486-AML-001 study data to Japan. This study is designed as a 2:1 randomization of CC-486 or placebo to assess the efficacy and safety of maintenance treatment with oral azacitidine in a cohort

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of Japanese participants ≥ 55 years with AML and in CR/CRi after conventional induction chemotherapy with or without consolidation chemotherapy. The primary endpoint is RFS because CC-486-AML-001 has successfully shown survival benefit for not only OS but RFS when compared with best supportive care (BSC). The CC-486 dose that has demonstrated tolerability and shown signs of clinical activity in the ORACLE Study is 200 mg. The primary endpoint of RFS and secondary endpoints of OS, time to relapse from CR/CRi, time to discontinuation from treatment, safety, pharmacokinetics (PK), and health-related quality-of-life (HRQoL) will be evaluated and allow for a comprehensive investigation of efficacy, exposure/safety, and HRQoL appropriateness of the clinical recommended dose for the Japanese population in comparison with the data from the Study CC-486-AML-001.

3.2 Background

Acute Myeloid Leukemia

Leukemia is a neoplastic proliferation of hematopoietic cells. These cells are either at undifferentiated or partially differentiated stages of maturation. As a consequence of excessive proliferation of the immature precursors, these cells eventually replace the normal blood-forming elements of the bone marrow, resulting in neutropenia, anemia, and thrombocytopenia. Acute myeloid leukemia (AML) can occur at any age and accounts for one-third of the leukemias diagnosed in patients >20 years. Incidence increases with age, with the median age at time of diagnosis around 68 years and the median age at time of death around 72 years[3 4]. In individuals ≥ 65 years, the incidence of AML is almost 10 times higher than in those < 65 years (17 per 100,000 versus 1.8 per 100,000, respectively)[5]. In Japan, the number of AML patients is estimated to be about 7,000 in 2017[6]. The incidence of AML in Japan is estimated to be 2 to 3 per 100,000, and the incidence increases with age in Japan as in the US.[7]

Two classification systems have been used for defining AML. In the classic French-American-British (FAB) system, morphology (based primarily on cytochemistry) defines the level of maturation and differentiation of the blasts; the threshold between myelodysplasia and AML is arbitrarily drawn at 30% blasts. Eight subtypes of AML have been described and are named according to the involved cell type. The more recent World Health Organization (WHO) classification seeks to further refine differences in leukemia biology by incorporating cytogenetic information, prior history of myelodysplasia, or therapy with certain chemotherapy agents or radiation therapy and presence of dysplasia[8].

More recently, the prognostic risk in AML is determined not only by cytogenetic abnormalities, (ie, chromosomal deletions, duplications, or translocations) but also by several somatic molecular alterations (gene mutations)[2]. The molecular genetic landscape of AML is complex, and several genes like CEBPA, NPM1, FLT3, RUNX1, P53, and ASXL1 are now part of risk assessments of AML patients. The current European LeukemiaNet (ELN) favorable risk criteria include t(8;21)(q22;q22.1); RUNX1-RUNX1T1; inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11. Normal cytogenetics portends intermediate-risk AML. AML that is often characterized

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by deletions of the long arms (monosomies) of chromosomes 5 or 7; by translocations or inversions of chromosome 3, t(6;9), t(9;22); or by abnormalities of chromosome 11q23 have particularly poor prognoses with chemotherapy. Acute myeloid leukemia may also arise secondary to previous cytotoxic chemotherapy or arise through transformation from existing myelodysplasia. Therapy-related AML arising from exposure to environmental toxins, cytotoxic drugs, or radiation currently accounts for about 10% to 30% of all cases of AML[9]. It is estimated that 35% to 40% of patients with myelodysplastic syndromes (MDS) will develop AML, with the disease often refractory to current therapy[10].

Current AML Treatments

The standard treatment modality for AML is chemotherapy globally, including in Japan. The therapeutic approaches are usually divided into two phases: induction of remission and post-remission (consolidation) therapy. For more than 30 years, the combination of cytarabine and an anthracycline has been the mainstay of treatments to induce remission[11 12]. The induction of remission therapy in leukemia is designed to produce rapid restoration of normal bone marrow function. A common induction regimen consists of cytarabine 100 mg/m^2/day for 7 days combined with daunorubicin 60 to 90 mg/m^2/day for 3 days, often referred to as the "7+3 protocol." With the combination of cytarabine and daunorubicin or their analogues, a CR, conventionally defined by the presence of < 5% blasts in the bone marrow together with recovery of peripheral-blood absolute neutrophil and platelet counts, can be achieved in up to 60% to 80% of adults with de novo AML who are < 60 years[11 12]. If CR is achieved, there are three basic treatment choices for post-remission therapy: additional chemotherapy, stem cell transplantation from a donor (allogeneic stem cell transplantation), or stem cell transplantation using the patient's own stem cells (autologous stem cell transplantation). For post-remission chemotherapy, the same chemotherapy agent used for remission induction is often repeated for one or more cycles, referred to as consolidation chemotherapy. When several courses of consolidation are given, survival rates at 2 to 3 years are 35% to 50% for young to middle-aged (< 65 years) adults who have achieved CR[13]. However, consolidation or post-remission chemotherapy for elderly (≥ 65 years) patients with AML has not been proven beneficial.

In elderly patients with AML, conventional cytotoxic intensive chemotherapy has been associated with CR rates of approximately 45%, considerably lower than in younger (< 60 years) patients. Unfortunately, the duration of remission is shorter, the early treatment-related mortality is high (approximately 30% to 50%)[14], which in part explains a median survival time between 9 to 12 months[15 16]. The standard consolidation chemotherapy regimens are not associated with prolonged CR in this elderly age group[17].

When standard chemotherapy (consolidation after remission induction) is given to patients < 65 years, the 5-year survival rate is 48%[18]. The 4-year survival rate is reported to be approximately 20% for patients aged 65 to 80 years[19]. In Japan, the basic treatment regimen is the same as the above-mentioned treatment regimen outside Japan. For elderly patients, the general conditions and the presence/absence of complications are taken into account when deciding whether induction

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therapy should be indicated and when determining the dose of chemotherapy once induction therapy is indicated. If considered to fit the standard treatment, these patients receive induction therapy, as do younger patients. If remission is achieved, patients receive allogeneic HSCT if eligible or consolidation therapy or chemotherapy depending on prognostic factors. If remission cannot be achieved, salvage therapy. will be performed[20]. CC-486 maintenance therapy was added as one option (Category 2B) in the NCCN Clinical Practice Guideline based on the result of the Study CC-486-AML-001[21]; however, maintenance therapy has not been established in Japan[22], and until recently, there is no standard for maintenance therapy. Patients who are not candidates for intensive remission induction therapy, such as older adult patients, are treated with low-dose cytarabine, injectable azacitidine with venetoclax, or new drugs[16 23].

CC-486 (Oral Azacitidine)

Azacitidine is an analog of the naturally occurring pyrimidine nucleoside cytidine and is classified as an antimetabolite. Vidaza® (injectable azacitidine) is approved by the US Food and Drug Administration (FDA) for the following 5 subtypes of the French-American-British (FAB) classification system of MDS: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). Vidaza is also approved by the European Commission for the treatment of adult participants who are not eligible for HSCT with intermediate-2 and high-risk MDS according to the Revised International Prognostic Scoring System (IPSS-R); CMML with 10% to 29% marrow blasts without myeloproliferative disorder; AML with 20% to 30% blasts and multi-lineage dysplasia according to World Health Organization (WHO) classification; and AML with >30% blasts according to WHO classification.

Azacitidine has been extensively studied in MDS and has been shown in a large, randomized Phase 3 trial of higher-risk MDS participants to provide a survival advantage of 9.4 months over conventional care regimens, thus altering the natural course of MDS. The median overall survival (OS) of azacitidine-treated participants was 24.5 months compared with 15.0 months for the combined conventional care regimen group, which included best supportive care (BSC), low-dose cytarabine, and intensive chemotherapy[24]. Silverman et al[25], using WHO AML criteria for diagnosis, reported a median OS of 19.3 months (n=27) in azacitidine-treated participants compared with 12.9 months (n=25) in participants who received BSC. More recently, a multicenter, randomized, Phase 3 study in untreated AML participants reported a CR rate of 27.8% and a clinically meaningful improvement in OS. The median OS was longer for participants treated with azacitidine at 10.4 months compared to those who received conventional care regimens at 6.5 months[26]. All of the above-mentioned studies used the standard azacitidine dose of 75 mg/m^2/day subcutaneous (SC) for 7 days of each 28-day cycle[27].

The QUAZAR Study (CC-486-AML-001) has demonstrated that CC-486 maintenance therapy was associated with significantly longer overall and relapse-free survival than placebo among older patients with AML who were in remission after chemotherapy. CC-486 was approved in the

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US and Canada in September 2020 and January 2021, respectively, and is indicated for continued treatment of adult patients with AML who achieved first CR/CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy[28]. An oral formulation of azacitidine (CC-486) has been developed and is currently being evaluated in clinical trials, either as a single agent or in combination with other drugs, for the treatment of hematological and solid malignancies. This oral formulation of azacitidine provides an opportunity for administration in a more convenient outpatient setting rather than in the hospital/clinic setting. Home administration also alleviates the morbidity of injection and catheter-site reactions and avoids the inconvenience and resource utilization costs associated with frequent hospital/clinic visits.

Results from the ongoing Phase 3, randomized, double-blind, placebo-controlled QUAZAR Study (CC-486-AML-001), which enrolled de novo AML and secondary AML participants, have shown that CC-486 (300 mg/day for 14 days of 28-day treatment cycles) as first-line maintenance therapy demonstrated significant and clinically meaningful improvement in OS and relapse-free survival (RFS) in AML in remission following induction chemotherapy with or without consolidation. Median follow-up was 41.2 months. Median OS was 24.7 months with CC-486 versus 14.8 months with placebo (P=0.0009; HR 0.69 [95% CI 0.55, 0.86]). Median RFS was 10.2 months in the CC-486 arm compared to placebo at 4.8 months (P=0.0001; HR 0.65 [95% CI 0.52, 0.81])[29]. The RFS rate at the 6-month time point was 67.4% in the CC-486 group and 45.2% in the placebo group, for a difference of 22.2%. The RFS rates were consistently higher for the CC-486 group than for the placebo group at each of the later time points (44.9% versus 27.4% at the 1-year time point and 26.6% versus 17.4% at the 2-year time point, respectively).

3.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of CC-486 may be found in the Investigator's Brochure (IB).

3.3.1 *Risk Assessment*

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Known/potential safety risks	The known side effects associated with azacitidine treatment as very common (a 10% or more chance that this will happen) are: anemia, neutropenia, leukopenia, febrile neutropenia, thrombocytopenia, bronchitis, cellulitis, pneumonia, oral fungal infection, skin infection, respiratory tract infection, upper respiratory tract infection, urinary tract infection, nausea, vomiting, diarrhea,	Patients should be monitored closely and appropriate actions taken following recommendations in Section 7.4.1.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	abdominal pain, upper abdominal pain, abdominal discomfort, constipation, asthenia, fatigue, malaise, pyrexia, nasopharyngitis, pharyngitis, laryngeal pain, decreased appetite, weight decreased, hypokalemia, arthralgia, back pain, bone pain, myalgia, musculoskeletal pain, pain in extremity, chest pain, dizziness, headache, insomnia, dyspnea, dyspnea exertional, rash, skin lesion, pruritus, ecchymosis, hematoma, petechiae, and epistaxis.	
Study Procedures		
Study design	Lower dose may not be able to show the comparable results with AML-001study in spite of consistently observed equivalent exposure of 200 mg in Japanese participants as 300 mg in Caucasian participants.	Although the feasible number of subjects is limited, subjects are enrolled as many as possible. And evaluate comprehensively that the results of not only the primary endpoint but also the secondary endpoints and safety are at least not substantially inconsistent with the results of AML-001 study and also assess in detail the efficacy and safety for individual subjects.
Study design	Small sample size may not be able to show the comparable results with AML-001study.	Although the feasible number of subjects is limited, subjects are enrolled as many as possible. And evaluate comprehensively that the results of not only the primary endpoint but also the secondary endpoints and safety are at least not substantially inconsistent with the results of AML-001 study and also assess in detail the efficacy and safety for individual subjects.
Study execution	It may take time to enroll the target population for the following reasons: • anticipated limited number of patients who are fit for intensive chemotherapy but not allogeneic SCT (such intensive chemotherapy is for patients who are usually fit for allogeneic SCT as well) • setting a placebo-control arm	• Carefully choose the study sites with high motivation to join this study and have recently shown good performance in hematologic malignancy studies. • Disseminate messages of CC-486-AML-001 study results as much as possible to encourage investigators and participants for this study.

Abbreviations: mRFS, median relapse-free survival; SCT, stem cell transplantation

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3.3.2 *Benefit Assessment*

Benefit considerations may include:

- Prolongation of RFS in the maintenance setting of CC-486 compared with BSC.
- Contribution to provide actual evidence in Japanese participants with AML in complete remission (ie, whether similar benefit can be expected in Japanese participants).

3.3.3 *Overall Benefit/Risk Conclusion*

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with CC-486 are justified by the anticipated benefits that may be afforded to participants with AML.

The Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis. This evaluation will be based on all available data – with particular attention to AEs or other safety trends in this or any other clinical study of CC-486 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury.

If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate health authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints	Estimands
Primary Objective	**Primary Endpoint**	**Primary Estimand**
• To evaluate the efficacy of CC-486 as maintenance therapy by using RFS in Japanese participants ≥ 55 years with AML who have achieved first CR or CRi after induction with intensive chemotherapy with or without consolidation chemotherapy.	• RFS	• Population: All randomized Japanese participants ≥ 55 years with AML, who have achieved first CR or CRi after induction with intensive chemotherapy with or without consolidation chemotherapy. • Treatment: CC-486 +/- BSC vs placebo +/- BSC as randomized • Intercurrent events: Participants without documented relapse at the time of study closure and participants who are withdrawn for any reason or start subsequent therapy will be censored. • Summary statistics: Kaplan-Meier curves, and hazard ratios from Cox

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Table 4-1: Objectives and Endpoints

Objectives	Endpoints	Estimands
		proportional hazards model with confidence interval.

Secondary
• To determine the effect of CC-486 as maintenance therapy on OS, time to relapse from CR/CRi, and time to discontinuation from treatment
• To determine safety and tolerability
• To determine PK
• To determine the effect of oral azacitidine on HRQoL
	Secondary
	• OS
	• 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)
	• PK parameters
	• Participant-reported outcomes utilizing the FACIT-Fatigue Scale and the EQ-5D-5L
		• Population:
		  • OS, time to relapse from CR/CRi, time to discontinuation from treatment, and HRQoL: All randomized Japanese participants ≥ 55 years with AML who have achieved first CR or CRi after induction with intensive chemotherapy with or without consolidation chemotherapy.
		  • Safety/tolerability: All treated participants
		  • PK parameters: All participants with PK sampling with CC-486 treatment
		• Treatment:
		  • OS, time to relapse from CR/CRi, time to discontinuation from treatment, safety/tolerability, and HRQoL: CC-486 +/- BSC vs placebo +/- BSC as randomized
		  • PK parameters: CC-486 +/- BSC
		• Intercurrent events:
		  • OS: Lost to follow-up or all other intercurrent events
		  • Time to relapse from CR/CRi: Death or start of subsequent therapy
		  • Time to discontinuation from treatment: Relapse, death, or start of subsequent therapy
		  • Safety/tolerability, PK parameters and HRQoL: All intercurrent events (eg, start of subsequent therapy) will be handled with treatment policy (ie, use information after intercurrent event)
		• Summary statistics:
		  • OS, time to relapse from CR/CRi, and time to discontinuation from treatment: hazard ratio from Cox proportional hazards model with confidence interval

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Table 4-1: Objectives and Endpoints

Objectives	Endpoints	Estimands
		• Safety/tolerability: Proportion of patients with event within treatment arms • PK parameters: PK parameters in CC-486 arm • HRQoL: Difference of HRQoL change from baseline scores within treatment arms
Exploratory • To determine plasma concentration of azacitidine and explore exposure-response relationships of efficacy and safety endpoints • To determine cytogenetic status as indicator of pending AML relapse • To evaluate molecular and/or cellular markers in the blood and bone marrow post induction and during maintenance therapy that may be predictive of clinical outcomes with oral azacitidine, including OS and RFS, following CR/CRi	**Exploratory** • Correlative analyses to assess the relationships between azacitidine exposure and safety, efficacy, and exploratory pharmacodynamic endpoints (eg, DNA methylation) • Analysis of genetic alterations, including gene sequencing for recurrent gene aberrations in AML • Flow cytometric analysis of hematopoietic cell immunophenotypes - MRD	

Abbreviations: AE, adverse event; AML, acute myeloid leukemia; BSC, best supportive care; CR, complete remission; CRi, complete remission with incomplete blood count recovery; DNA, deoxyribonucleic acid; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; IgG, immunoglobulin G; MRD, minimal residual disease; OS, overall survival; PK, pharmacokinetic(s); RFS, relapse-free survival.

5 STUDY DESIGN

5.1 Overall Design

This is a multicenter, placebo-controlled, Phase 2 study with a double-blind, randomized, 2:1 group design in Japanese participants 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 Screening Phase, the Treatment Phase, and the Follow-up Phase. The study design schematic is presented in Figure 5.1-1.

Approximately 15 participants will be randomized 2:1 to CC-486 or placebo.

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- Approximately 10 participants will receive CC-486.
- Approximately 5 participants will receive placebo.

After informed consent is obtained, participants will undergo screening procedures to determine eligibility (28 days for screening). Eligible participants will be dynamically randomized using an Interactive Response Technology (IRT) by the following factors:

1. Age: 55 to 64 years/ ≥65 years
2. Prior history of MDS/CMML: Yes/No
3. Cytogenetic risk: Intermediate/Poor
4. Consolidation therapy: Yes/No

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, participants will ingest Investigational Product (IP) (CC-486 tablets or placebo tablets) for the first 14 days of each 28-day cycle. Dose modifications may occur for managing toxicity if necessary during treatment (Section 7.4.1).

During the Double-blind Treatment Phase, participants 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, physical examination, vital signs and weight measurement, Eastern Cooperative Oncology Group (ECOG) performance status, hematology and serum chemistry, pregnancy testing (women of childbearing potential [WOCBP] 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, and HRQoL.

A separate central review of all bone marrow aspirates, bone marrow biopsies, and peripheral blood smears will be conducted by a pathologist blinded to participant 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 participant, a third-party reviewer will adjudicate and make the final assessment.

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

In participants 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 (Section 7.4.2).

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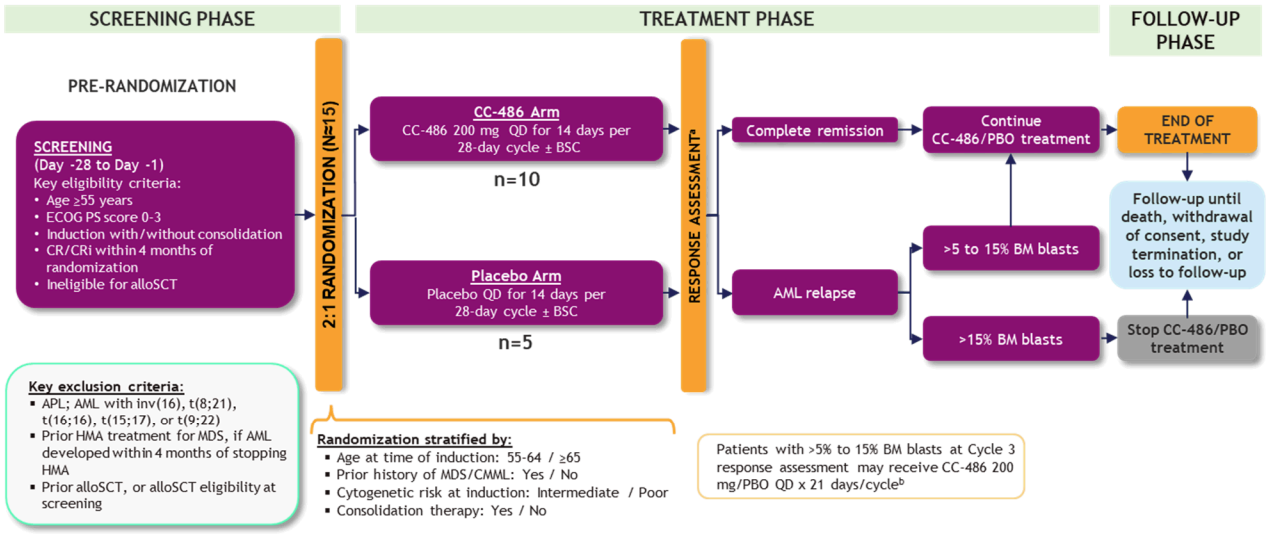
Participants will be discontinued from treatment when they meet the following criteria:

- Appearance of > 15% blasts in the bone marrow or peripheral blood.
- 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).

All discontinued participants, regardless of reason for discontinuation, should undergo Treatment Discontinuation Visit procedures at the time of study discontinuation. Participants 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, participants 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, until a participant is lost to follow-up or study end, or when the commercial product of CC-486 becomes available at the site, whichever comes first.

Figure 5.1-1: Study Design Schema



[a]IWG 2003; assessment for CR/CRi or relapse at the Cycle 3; if CC-486 treatment continues, response assessed every 3rd cycle (ie, Cycles 6, 9, 12, etc).
[b]For participants receiving the initially assigned dose level and schedule.
alloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BM, bone marrow; BSC, best supportive care; CMML, chronic myelomonocytic leukemia; CR, complete remission; Cri, complete remission with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agent; IWG, International Working Group; MDS, myelodysplastic syndrome; OS, overall survival; PBO, placebo; QD, once daily

5.1.1 *Data Monitoring Committee and Other Committees*

A Data Monitoring Committee or other review committee will not be used in the study.

5.2 Number of Participants

Approximately 15 participants will be randomized 2:1 to receive CC-486 or placebo.

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5.3 End of Study Definition

The start of the trial is defined as the first participant first visit. End of trial is defined as the last participant last visit. Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if this is not the same.

A participant is considered to have completed the study if he/she has completed the last visit.

5.4 Scientific Rationale for Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study in Japanese participants ≥ 55 years with AML in CR/CRi following intensive induction therapy with or without consolidation therapy. Participants will be randomized 2:1 to receive 200 mg CC-486 (QD or placebo for the first 14 days of each 28-day treatment cycle. This is a bridging study to provide clinical data that will allow extrapolation of the CC-486-AML-001 study data to Japan.

One of the most important goals of maintenance therapy for AML should be to minimize the risk of relapse and sustain complete remission as long as possible. Study CC-486-AML-001 has shown survival benefit on not only OS but RFS when compared with BSC, and the subgroup analyses of the primary endpoint (OS) and key secondary endpoints (RFS) showed a consistent efficacy benefit of CC-486 across various demographic and disease-related subgroups. Thus, in Study CA055-005, RFS is set as a primary endpoint and OS as a secondary endpoint.

When designing CA055-005 as a randomized, placebo-controlled study, the data of median RFS from both arms of Study CC-486-AML-001 (ie, 10.2 months vs 4.8 months for the CC-486 arm and BSC arm, respectively) were primarily referred to for the statistical sample size calculation.

The target population of this study should be same as that of Study CC-486-AML-to secure comparability between the 2 studies for the purpose of bridging. As for the target age, although most enrolled participants will be elderly (eg, ≥ 60 years or ≥ 65 years), the same target age is set as in Study CC-486-AML-001 (ie, ≥ 55 years) because the survival benefit in Study CC-486-AML-001 was observed regardless of age group.

The 2:1 randomization to CC-486 or placebo will be performed to adequately secure the number of participants in the CC-486 group and to keep the number of participants in the placebo group to a minimum. Best supportive care will include but not be limited to red blood cell (RBC) and platelet transfusions; use of an erythropoiesis-stimulating agent (ESA); antibiotic, antiviral, and antifungal therapy; nutritional support; and granulocyte-colony stimulating factors (G-CSFs) for participants experiencing neutropenic infections. Thus the risk of not providing participants with appropriate care is minimized while providing the potential benefit of maintaining CR/CRi status.

The starting dose for participants is 200 mg CC-486 or placebo QD for the first 14 days of each 28-day treatment cycle. This CC-486 dose and schedule have demonstrated tolerability and shown signs of clinical activity in a prior study the ORACLE study. Participants should continue to receive CC-486 for at least 2 cycles of treatment before being assessed for discontinuation from the study due to disease relapse at the early timing of efficacy evaluation.

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5.4.1 *Participant Input Into Study Design*

Not applicable.

5.5 Justification for Dose

In Study CC-486 AML-001, the dose and schedule of 300 mg CC-486 orally administered QD for the first 14 days of every 28-day treatment cycle were selected based on cumulative safety, efficacy, tolerability, and biologic data observed in a recently concluded Phase 1/2 study (AZA PH US 2007 CL 005)[30 31].

Study AZA PH US 2007 CL 005 was initially designed to determine the maximum tolerated dose of CC-486 administered according to different treatment schedules and to evaluate the pharmacokinetic behavior of azacitidine administered by both oral and SC routes. In Part 2 of the AZA PH US 2007 CL 005, following administration of a 200-mg or 300-mg dose, areas under the curve (AUCs) were measured on Day 1 and on the last day of dosing (ie, Day 14 or Day 21), and then the mean AUC (between Day 1 and Day 14 or 21) was calculated. Finally, the mean extrapolated cumulative azacitidine exposure per cycle was calculated by multiplying the mean AUC by the number of dosing days in the treatment cycle (ie, 7, 14, or 21). Similar calculations were made for the SC route. The results of the study (AZA PH US 2007 CL 005 Clinical Study Report) showed that, compared with SC treatment (75 mg/m^2 QD × 7 days), CC-486 300 mg QD × 14 days and 21 days provides cumulative exposure per cycle of 38% and 57%, respectively.

The 300-mg QD × 14 days regimen in Study CC-486-AML-001 has also been determined to be biologically active (maintaining hypomethylation at the end of treatment cycle at the 28th day) and was associated with hematological responses in ~31% of participants treated in Study AZA PH US 2007 CL 005. This regimen is also generally well tolerated. Furthermore, this schedule may allow participants to remain on study for protracted periods. In particular, with the shorter schedule of a 14-day QD regimen (vs the 21-day QD regimen studied in the Study AZA PH US 2007 CL 005), participants may have a better observance to treatment and better long-term tolerance to CC-486, particularly because gastrointestinal dysfunction is common in this patient population after undergoing induction therapy for AML. As the CC-486-AML-001 is a maintenance study and as participants would be in CR/CRi at study entry with intent to suppress relapse occurrence and continue on therapy for up to more than years, the appropriate starting dose and schedule was deemed to be 300 mg QD x 14 days of every 28-day cycle.

Although a clear reason has not yet been elucidated, it has been demonstrated consistently that exposure of CC-486 is different between Japanese and non-Japanese participants. As far as the Japanese population is concerned, two Phase 1 studies have been conducted in Japanese participants with hematologic malignancy (AZA-MDS-005 and CC-486-MDS-001). In the MDS-005, conducted in Japanese participants with MDS, all 4 participants who were evaluated for dose-limiting-toxicity discontinued the study treatment due to serious adverse event (SAE) (severe neutropenia/infection) when CC-486 was given as a QD dose of 300 mg for 21 days/28-day cycle. The exposure of 300 mg for 21 days for Japanese participants in AZA-MDS-005 was indicated to be higher when compared with that for Caucasian participants. Study CC-486-MDS-001 was accordingly planned to start with a lower dose cohort (ie, 100 mg for 14 days/28 day-cycle). This

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study was terminated due to the unexpectedly lower enrollment in this lower dose cohort, but it was again indicated that the exposure of 100 mg (14 days/28 day-cycle) in Japanese participants was higher and almost within the range of that of 200 mg in Caucasian participants. Taking into consideration accumulated PK and safety data in Japanese participants, the safety run-in was first conducted in Japanese participants by the dose-escalation from 100 mg to 200 mg (14 days/28 day-cycle) to determine a recommended Phase 3 dose for Asian (including Japanese) participants in the Global Phase 3 study. As a result, the 200-mg dose (14 days/28 day-cycle) for angioimmunoblastic T-cell lymphoma (ORACLE Study) was recommended by the Independent Data Monitoring Committee (IDMC) and chosen as a Phase 3 dose for Asian (including Japanese) participants based on the safety, tolerability, and PK profiles, where the exposure of 200 mg for 14 days in Japanese participants were indicated to be comparable with 300 mg for 14 days in Caucasian participants.

Based on these data, the dose and schedule of 200 mg CC-486 orally administered QD for the first 14 days of every 28-day treatment cycle were selected for evaluation in the current study.

6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

b) Participants must be able to adhere to the study visit schedule and other protocol requirements.

2) Type of Participant and Target Disease Characteristics

a) Newly diagnosed, histologically confirmed *de novo* AML or AML secondary to prior MDS or CMML.

b) Participants should have undergone induction therapy with intensive chemotherapy with or without consolidation therapy as recommended in appropriate guideline(s) or equivalent regimen according to institutional standard: 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	• < 5% blasts in bone marrow • absence of blasts with Auer rods • absence of extramedullary disease • independent of blood transfusions

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• peripheral neutrophil count ≥ 1.0 x 10^9/L • platelet count ≥ 100 x 10^9/L	• peripheral neutrophil count < 1.0 x 10^9/L or platelet count < 100 x 10^9/L

c) ECOG performance status of 0, 1, 2, or 3.

3) Age of Participant

Participant must be ≥ 55 years of age inclusive at the time of signing the informed consent.

4) Reproductive Status

a) A Women of childbearing potential (WOCBP) is a female who: 1) has achieved menarche at some point; 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) 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) and must

i) Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy and must agree to ongoing pregnancy testing during the study and after end of study therapy. This applies even if the participant practices true abstinence* from heterosexual contact.

ii) Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, highly effective contraception without interruption - 28 days prior to starting investigational product, during study therapy (including dose interruptions), and for 6 months after discontinuation of study therapy, or longer if required by local regulations. Contraception requirements are detailed in Appendix 4.

b) Male participants must practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for at least 3 months following investigational product discontinuation, or longer if required by local regulations, even if the male participant has undergone a successful vasectomy.

** True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.*

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Medical Conditions

a) 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

b) 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

c) Prior bone marrow or stem cell transplantation

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d) Candidate for allogeneic bone marrow or stem cell transplant at screening
e) Have achieved CR/CRi following therapy with hypomethylating agents
f) Received therapy with hypomethylating agents for MDS and went on to develop AML within four months of discontinuing therapy with hypomethylating agents
g) Proven central nervous system leukemia
h) Diagnosis of malignant disease within the previous 12 months (excluding basal cell carcinoma of the skin without complications, carcinoma in situ of the cervix or breast, or other local malignancy excised or irradiated with a high probability of cure)
i) Unstable angina, significant cardiac arrhythmia, or New York Heart Association Class 3 or 4 congestive heart failure
j) Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment)
    i) In the case of prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, symptoms must have completely resolved and based on Investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

2) Prior/Concomitant Therapy

a) Participant used any investigational agents or therapy within 28 days or 5 half-lives prior to Day 1 of Cycle 1, whichever is longer
    i) Participants currently in other interventional or investigational vaccine trials may not participate in Bristol-Myers Squibb (BMS) clinical trials until the washout period is achieved.
b) Participant has received live attenuated vaccines or live COVID-19 vaccines within 30 days prior to initiation of study treatment
c) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7: Concomitant Therapy.

3) Physical and Laboratory Test Findings

a) Participant has any of the following laboratory abnormalities:
    i) Absolute neutrophil count (ANC) < 0.5 x 10^9/L
    ii) platelet count < 20 x 10^9/L
    iii) Serum bilirubin > 1.5 times the upper limit of normal (ULN)
    iv) Serum aspartate aminotransferase or alanine aminotransferase > 2.5 times the ULN
    v) Serum creatinine > 2.5 times the ULN
b) Known active viral infection with known human immunodeficiency virus (HIV) or active chronic hepatitis B virus (HBV) or hepatitis C virus (HCV)
    i) Participants who are hepatitis B surface antigen (HBsAg) negative and HBV viral DNA negative are eligible
    ii) Participants who had hepatitis B but have received an antiviral treatment and show nondetectable viral DNA for 6 months are eligible
    iii) Participants who are seropositive because of HBV vaccine are eligible

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iv) Participants who had HCV infection but have received an antiviral treatment and show no detectable HCV viral RNA for 6 months are eligible

4) Allergies and Adverse Drug Reaction

a) Known or suspected hypersensitivity to azacitidine or mannitol

5) Other Exclusion Criteria

a) Participant has any significant medical condition, active infection (including SARS-CoV-2 suspected or confirmed), laboratory abnormality, or psychiatric illness that would prevent participation in the study.

i) In the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

(1) A participant who is excluded for SARS-CoV-2 infection could be rescreened.

(2) Additionally, a participant who is currently in another interventional trial for COVID-19 may not participate in this clinical trial until the protocol-specific washout period is achieved.

b) Participant has received live attenuated vaccines or live COVID-19 vaccines within 30 days prior to initiation of study treatment

c) Participant is unwilling or unable to complete patient-reported outcome assessments without assistance or with minimal assistance from trained site personnel and/or caregiver

d) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)

e) Any condition, including the presence of laboratory abnormalities, which places the participant at unacceptable risk if he/she were to participate in the study

f) Any significant medical condition, laboratory abnormality, or psychiatric illness that would interfere with or prevent participation in the study

g) Any condition that confounds the ability to interpret data from the study

h) Any condition causing an inability to swallow tablets

i) Any condition that would impair absorption of the study medication (ie, short gut, malabsorption syndrome)

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

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6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 *Retesting During Screening or Lead-in Period*

Retesting of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to randomization is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Participants who fail eligibility criteria due to low neutrophil count or platelet count or other laboratory abnormality can be rescreened as long as this occurs within 4 months (± 7 days) from the achievement of CR or CRi status.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s), or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as IPs/AxMPs. Not applicable for this study.

7.1 Study Interventions Administered

The selection and timing of dose for each participant is as follows:

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Table 7.1-1: Study Interventions

Arm Name	CC-486	Placebo
Intervention Name	CC-486	Placebo for CC-486
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	200 mg/150 mg	200 mg/150 mg
Dosage Level(s)	200 mg taken for the first 14 days of each 28-day treatment cycle	200 mg taken for the first 14 days of each 28-day treatment cycle
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP and Non-IMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in blister cards. Each blister card will be labeled as required per country requirement.	Study intervention will be provided in blister cards. Each blister card will be labeled as required per country requirement.

Abbreviations: AxMP, auxiliary medicinal product; IMP, Investigational Medicinal Product.

Antiemetic medication (not supplied by the Sponsor) may be administered 30 minutes prior to each IP dose. Participant will ingest IP with approximately 240 mL of room temperature water. Investigational product may be taken on an empty stomach or with food. If IP is taken in the morning, participants may consume their usual breakfast before or after administration.

7.1.1 *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 be limited to RBC and platelet transfusions; use of an ESA; antibiotic, antiviral, and antifungal therapy; nutritional support (Section 7.7); and granulocyte-colony stimulating factors (G-CSFs) for participants experiencing neutropenic infections (Section 7.7). Thus, the risk of not providing participants with appropriate care is minimized while providing the potential benefit of maintaining CR/CRi status.

7.2 Method of Study Intervention Assignment

Study using Interactive Response Technology (IRT): All participants will be centrally randomized using IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

Study intervention will be dispensed at the study visits as listed in the Schedule of Activities (Section 2).

Enrolled participants, including those not dosed, will be assigned sequential participant numbers. Sequential numbering may restart for each participating site because the distinct patient identification number will ultimately comprise the site number and participant number. Those

enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

Participants approved for enrollment will be dynamically randomized to receive CC-486 or placebo in a 2:1 ratio. Randomization will be accomplished by an IRT to ensure timely registration and randomization. Based on an allocation ratio preserving biased coin minimization, participants will be stratified by age at time of induction therapy (55 to 64 years or ≥ 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)[32]. The random treatment assignment will be concealed so that investigators and participants will not know in advance the next treatment assignment.

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

7.3 Blinding

This is a double-blind study. Access to treatment codes will be restricted from all participants, and site and Sponsor personnel prior to primary database lock with exceptions as specified below.

Blinding of study treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving the IP. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding after the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is IRT.

For information on how to unblind in an emergency, consult the IRT Manual.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to minimize additional disclosure and the impact of unblinding.

Any request to unblind a participant for nonemergency purposes should be discussed with the Medical Monitor.

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the IRT and is capable of breaking the blind through the IRT system without prior approval

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from the Sponsor. Following the unblinding, the Investigator shall notify the Medical Monitor or designee that the unblinding took place.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.A scientist in the Bioanalysis department of BMS (and/or a designee in the external bioanalytical laboratory) will be unblinded to the randomized treatment assignments to minimize unnecessary bioanalytical analysis of samples. Any results shared by the Bioanalysis group with the Sponsor's study team will be blinded to ensure integrity of the study.

7.4 Dosage Modification

7.4.1 *Dose Modifications for Toxicity*

Participants should be monitored for toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0, 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 150 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 participants 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 participant's treatment schedule from 14 to 7 days (21 days to 14 days for those participants whose dose schedule has been extended due to disease progression) should first be discussed with the Medical Monitor or designee. Participants should not receive less than 150 mg IP or be scheduled to receive treatment for less than 7 days.

Participants 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 150 to 200 mg.

Dose Modification for Febrile Neutropenia ≥ Grade 3

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Any participant who experiences ≥ Grade 3 febrile neutropenia (two consecutive readings of body temperature > 38.0°C for 2 hours and an ANC 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 participant experiences febrile neutropenia in 2 consecutive cycles, the steps noted above should be followed, but the IP dose should be reduced to 150 mg upon resumption of treatment with IP. A treatment schedule modification from 14 to 7 days (21 days to 14 days for those participants whose dose schedule has been extended due to disease progression) of treatment may be warranted if a participant experiences regular episodes of febrile neutropenia that are deemed by the Investigator to be related to IP.

Dose Modification for Diarrhea ≥ Grade 3

It is recommended that participants experiencing diarrhea be managed according to the guidelines provided in Appendix 7. Antidiarrheal medication may be administered as prophylaxis against diarrhea and for treatment of any AEs of diarrhea. Dose modifications for diarrhea are summarized in Table 7.4.1-1. For participants 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, the Investigator may choose to omit the antiemetic as required, provided this is clearly documented in the CRF. Dose modifications for nausea and vomiting are summarized in Table 7.4.1-1.

Dose Modification for Renal Dysfunction and Abnormal Serum Electrolytes

If unexplained elevations of blood urea nitrogen (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 150 mg in the next cycle of treatment. A schedule modification from 14 to 7 days (21 days to 14 days in those participants 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 participant 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 Table 7.4.1-1.

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 Table 7.4.1-1.

Table 7.4.1-1: Guidelines for Dose Modifications

NCI-CTCAE Toxicity Grade	Action
Febrile Neutropenia (≥ Grade 3)	• Continue CC-486 at the discretion of the Investigator – If episode persists for ≥ 4 days despite adequate / maximal antibiotic, antiviral, and/or antifungal therapy, CC-486 should be temporarily discontinued until the fever has resolved. – Resume CC-486 at the same dose after the fever has resolved and the ANC has improved or stabilized (as assessed by the Investigator). CC-486 should not be resumed for at least 3 days following resolution of fever. • If a participant experiences febrile neutropenia in 2 consecutive cycles, the steps noted above should be followed, but the CC-486 dose should be reduced to 150 mg upon resumption of treatment with CC-486. • If participant continues to experience febrile neutropenia episodes that are deemed to be related to CC-486 by the Investigator, a treatment schedule modification from 14 to 7 days (21 days to 14 days for those participants 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 CC-486 and provide adequate/maximum medical intervention. • Resume CC-486 at same dose when toxicity resolves to ≤ Grade 1. • If event reoccurs upon rechallenge or during next treatment cycle, reduce CC-486 dose to 150 mg. • If event reoccurs at same intensity once dose is reduced to 150 mg, follow the steps above and modify treatment schedule from 14 to 7 days (21 days to 14 days for those participants whose dose schedule has been extended due to disease progression) of CC-486 administration. (Treatment schedule modification requires prior discussion with Medical Monitor.)
Nausea and/or Vomiting (≥ Grade 3)	• Interrupt CC-486 and provide adequate/maximal medical intervention. • Resume CC-486 at same dose when toxicity resolves to ≤ Grade 1.

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Table 7.4.1-1: Guidelines for Dose Modifications

NCI-CTCAE Toxicity Grade	Action
	• If event reoccurs upon rechallenge or at same intensity during next treatment cycle, reduce dose to 150 mg. (Treatment schedule modification requires prior discussion with Medical Monitor.)
Renal Dysfunction	• For unexplained elevations of BUN and/or serum creatinine from baseline level (> 20%), hold CC-486 if this is apparent during the CC-486 administration phase and/or delay the start of the next cycle of treatment until values return to baseline (± 20%). Reduce CC-486 dose in the next cycle of treatment to 150 mg. • Discontinue CC-486 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 CC-486 dosing and provide medical intervention as appropriate. • Resume CC-486 at same dose when toxicity resolves to ≤ Grade 2. • If event reoccurs upon rechallenge or at same intensity during next treatment cycle, reduce CC-486 dose to 150 mg. • If event reoccurs at same intensity once dose is reduced to 150 mg, follow the steps above and modify treatment schedule from 14 to 7 days (21 days to 14 days for those participants whose dose schedule has been extended due to disease progression) of CC-486 administration. (Treatment schedule modification requires prior discussion with Medical Monitor.)

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; BUN, blood urea nitrogen; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

7.4.2 Dose and Schedule Adjustment in Participants with AML Relapse/Progression

In participants 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):

- Participant currently on blinded treatment of CC-486 200 mg or placebo QD for 14 days — escalate schedule to CC-486 200 mg or placebo QD for 21 days
- Participant currently on blinded treatment of CC-486 150 mg or placebo QD for 14 days — escalate dose schedule, as a first step, to CC-486 150 mg or placebo QD for 21 days and then escalate dose to CC-486 200 mg or placebo QD for 21 days

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- Participant currently on blinded treatment for CC-486 150 mg or placebo QD for 7 days - escalate dose schedule, as a first step, to CC-486 150 mg or placebo QD for 14 days and then escalate dose to CC-486 200 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.

7.4.3 *Re-treatment Criteria*

Prior to the start of each cycle, participants will have laboratory assessments performed to evaluate organ function. To proceed to the next cycle, participants must continue to meet entry criteria regarding renal and hepatic function (see Section 6.2). Thus, participants 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 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 participant 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 participant is experiencing clinical benefit. Justification for the participant continuing in the study must be recorded in the source documents.

Prior to discontinuing a participant for reasons other than those listed in Section 8.1, the investigator should contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

7.5 Preparation/Handling/Storage/Accountability

The IP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP/AxMP is only dispensed to study participants. The IP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

Study intervention not supplied by BMS will be stored in accordance with the package insert.

IP/AxMP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure the drug is accurately administered. This includes documentation of

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drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in Appendix 2.

7.6 Treatment Compliance

Study intervention compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

- When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets, etc during the site visits and documented in the source documents and relevant forms. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.
- A record of the quantity of CC-486 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

7.7 Concomitant Therapy

7.7.1 *Prohibited and/or Restricted Treatments*

All prior and concomitant medications (prescription and nonprescription) that are administered 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 CRF. Significant nondrug therapies and concomitant procedures administered following the first dose of IP through the last dose of IP or up to the Treatment Discontinuation Visit, whichever period is longer, must be recorded on the appropriate CRF.

Prior treatment with ESAs, thrombopoiesis-stimulating agents (TSAs), iron-chelation therapy, and other medications considered supportive care for AML should be recorded, regardless of discontinuation date of treatment.

Live COVID-19 vaccines should not be administered to a participant during the study, including during treatment, during the Safety Follow-up Period, and within 3 months following the last dose

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of IMP. In addition, the administration of a live COVID-19 vaccine is prohibited up to 30 days prior to initiation of study treatment.

Concomitant medications should be kept to a minimum during the study. However, if considered necessary for the participant's welfare and are unlikely to interfere with the IP, they may be given at the discretion of the investigator.

7.7.1.1 Permitted Concomitant Medications and Procedures

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 be limited to RBC and platelet transfusions; use of an ESA; antibiotic, antiviral, and antifungal therapy; nutritional support; and granulocyte-colony stimulating factors (G-CSFs) for participants experiencing neutropenic infections. Thus the risk of not providing participants with appropriate care is minimized. The use of these products will be considered as concomitant treatment and documented as concomitant medications, therapies, or procedures.

The use of myeloid growth factors, G-CSFs, and granulocyte macrophage colony-stimulating factors [GM-CSFs]) may be given per Investigator's discretion. For participants who develop an ANC $< 0.5 \times 10^9$/L, administration of prophylactic fluoroquinolone antibiotics (eg, ciprofloxacin or levofloxacin) or other prophylactic antibiotic treatments used as standard treatment at the site is allowed and must be documented as a concomitant medication on the appropriate CRF. If neutropenic infection occurs, treatment should consist of a broad-spectrum antibiotic, and if the Investigator deems the use of a myeloid growth factor to be medically important, myeloid growth factors may also be administered. If myeloid growth factors are administered, they should be stopped within 4 days following resolution of the febrile episode. In addition, the participant's response to protocol-defined treatment should not be assessed until at least 3 weeks following the last dose of myeloid growth factor to avoid confusing relapse of disease, when it may have been related to growth factor.

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. Pretreatment or post treatment with a serotonin (5-HT_3) receptor antagonist (or other antiemetic medication) will be considered as concomitant therapy and should be recorded on the appropriate CRF.

COVID-19 vaccines that have been authorized by an appropriate regulatory agency and are NOT live or attenuated (not capable of transmitting infectious virus) are acceptable and should be handled in the same manner as other vaccines approved for immunocompromised cancer subjects. COVID-19 vaccines that are NOT live can be administered during the study. If possible, Investigators are encouraged to give the vaccine at least 24 to 72 hours prior to starting study drugs (to watch for and manage vaccine-related acute toxicities).

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects who are taking the study drugs in this trial, are unknown.

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7.7.1.2 Prohibited Concomitant Medications and Procedures

The following concomitant medications are specifically **excluded** during the study:

- Cytotoxic chemotherapeutic agents or experimental agents
- Romiplostim and other TSAs (eg, interleukin-11)
- Hydroxyurea
- Lenalidomide
- Pomalidomide
- Thalidomide
- Arsenic trioxide
- Interferon
- Retinoids
- Live COVID-19 vaccines should not be administered to a participant during the study, including treatment, during the Safety Follow-up Period, and within 3 months following the last dose of IMP. In addition, the administration of a live COVID-19 vaccine is prohibited up to 30 days prior to initiation of study treatment.

7.7.2 *Other Restrictions and Precautions*

Participants are prohibited from joining another clinical trial while they are participating in this study.

7.8 Continued Access to Study Intervention After the End of the Study

At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study intervention for maximum treatment duration as specified in Section 7.1.

If the study treatment is not available as an approved and available treatment, study intervention will be provided via an extension of the study, a rollover study requiring approval by the responsible Health Authority and ethics committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of CC-486 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or other health program. In all cases, BMS will follow local regulations.

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8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention

Participants MUST discontinue IP (and Non-IP/AxMP at the discretion of the investigator) for any of the following reasons:

- Disease relapse

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

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

  – 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).
- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Participant withdraws from active treatment but continues follow-up
- Participant becomes eligible (per Investigator) for allogeneic bone marrow or stem cell transplantation during the treatment period
- Death
- Loss to follow up
- Protocol violation
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). Additionally, all participants who are discontinued from protocol-prescribed treatment will be followed for a period of 28 days following

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the last dose of IP or until the date of the last study visit, whichever is later, for the collection of AEs. Discontinued participants will not be replaced.

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 *Post-study Intervention Study Follow-up*

In this study, RFS is the primary endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 *Individual Discontinuation Criteria*

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If the investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the time frame defined in the Schedule of Activities.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

9.1 Efficacy Assessments

9.1.1 *Efficacy Assessment for the Study*

International Working Group Response

International Working Group (IWG) 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. Participants 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 at Screening, 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 aspirate 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 Manual 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 it is to be used for cytogenetics testing [refer to the Laboratory Manual for sample collection, handling, and processing instructions]).

Follow-up AML Therapies

All discontinued participants, regardless of reason for discontinuation, should be followed for subsequent AML therapies every month for the first year and every 3 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

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All discontinued participants, regardless of reason for discontinuation, should be followed for survival every month for the first year and every 3 months thereafter until death, loss to follow-up, withdrawal of consent from further follow-up, or study closure. The survival follow-up can be performed via telephone.

9.1.2 *Health-related Quality of Life*

The evaluation of patient-reported outcomes (PROs) is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the subject's perspective and offer insights into patient experience that may not be captured through physician reporting. Additionally, generic health-related quality of life (HrQoL) measures provide data needed for calculating utility values to inform health economic models. Health-related quality of life (HRQoL) instruments Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale and the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) will be completed by participants throughout the trial. The questionnaire should be completed by the participant before any clinical assessments are performed at any given visit (refer to Table 2-2 and Table 2-3). If a participant will not complete one or more questionnaires, the reason for this will be documented. Questionnaires should be completed in the language most familiar to each participant, and participants should be given adequate time and space to complete the questionnaire. If the participant withdraws from the study prematurely, all attempts should be made to obtain a final quality-of-life questionnaire prior to participant discontinuation.

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale is a subscale of the FACIT and has been validated in the oncology setting (Appendix 8)[33 34]. The items are measured on a response scale with five options (0 = not at all to 4 = very much) and has a 7-day recall period. The 13-question subscale has scores that range from 0 to 52, with higher scores indicating less fatigue. Quality of life scores on these FACIT scales significantly decline as patient performance status worsens. Interventions that reverse fatigue should have a positive effect on quality of life.

Participants' reports of general health status will be assessed using the EQ-5D-5L questionnaire (Appendix 9)[35]. The EQ-5D-5L has 2 components: a descriptive system and a visual analog scale (VAS). The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension describes 5 levels of problems, including "no," "slight," "moderate," "severe," and "extreme" or "unable to." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Thus, the numbers 11111 and 55555 represent the best health state and the worst health state, respectively, described by the EQ-5D-5L. Altogether, the instrument describes 5^5 = 3,125 health states. Empirically, derived weights can be applied to an individual's responses to the EQ-5D-5L to generate a utility index measuring the value to society of his or her current health. In addition, a VAS allows respondents to rate their own current health on a 101-point scale ranging from 0 = "worst imaginable" to 100 = "best imaginable." The EQ-5D-5L takes approximately 5 minutes to complete.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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AEs will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

Refer to Appendix 3 for SAE reporting.

9.2.1 *Time Period and Frequency for Collecting AE and SAE Information*

All SAEs and non-serious AEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 28 days following discontinuation of dosing or until the End of Treatment Visit, whichever is later.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure.

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 *Method of Detecting AEs and SAEs*

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

9.2.3 *Follow-up of AEs and SAEs*

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 *Regulatory Reporting Requirements for SAEs*

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 *Pregnancy*

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 6 months after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3. If a female partner of a male participant taking IP becomes pregnant within 3 months after the male participant's last dose of IP, the male participant taking IP should notify the Investigator, and the pregnant female partner should be advised to call her health care provider immediately.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

9.2.6 *Laboratory Test Result Abnormalities*

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE eCRF, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study intervention discontinued or interrupted

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- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia vs low hemoglobin value).

9.2.7 *Potential Drug-induced Liver Injury*

Drug-induced liver injury (DILI) has not been associated with CC-486. Specific criteria for identifying a potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

9.2.8 *Other Safety Considerations*

Any significant worsening of conditions noted during interim or final physical examinations, electrocardiogram, x-ray filming, or any other potential safety assessment required or not required by the protocol should also be recorded as a non-serious AE or SAE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3). If an overdose is associated with an AE, the overdose and AE should be reported as separate terms.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 *Physical Examinations*

Refer to Schedule of Activities.

9.4.2 *Vital Signs*

Refer to Schedule of Activities.

9.4.3 *Electrocardiograms*

Refer to Schedule of Activities.

9.4.4 *Clinical Safety Laboratory Assessments*

Investigators must document their review of each laboratory safety report.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology
Hemoglobin
Hematocrit
WBC count with differential
Absolute neutrophil count
Platelet count

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Table 9.4.4-1: Clinical Laboratory Assessments

RBC count	
MCV, MCH, MCHC	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Direct/indirect total bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Glucose	Total protein Albumin Sodium Potassium Magnesium Chloride Calcium Phosphorus Bicarbonate
Urinalysis	
A standard urinalysis (including microscopic analysis if indicated; screening and whenever clinically indicated in the Double-blind Treatment Phase)	
Viral Serology	
HBsAg, anti-HBs, anti-HBc, hepatitis C antibody, HIV antibody and, if applicable, HBV viral DNA and HCV viral RNA testing by PCR (screening)	
Other Analyses	
Coagulation, including PT, PTT, INR (screening)	
Unstained peripheral blood smear (screening, predose, discharge)	
Pregnancy test (WOCBP only: screening, predose, discharge)	

Abbreviations: DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PCR, polymerase chain reaction; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; RNA, ribonucleic acid; WOCBP, women of childbearing potential.

9.4.5 *Imaging Safety Assessment*

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment.

9.5 Pharmacokinetics

On the PK days (Cycle 1 Day 1 and Cycle 1 Day 14), participants will ingest CC-486 in the clinic after performing the required overnight fasting and pre-dose PK sample collection, with each dose being given at approximately the same time of day. The exact date and time of dosing and PK sampling will be recorded in the source documents and appropriate form. The following PK parameter values will be derived by noncompartmental methods by a validated PK analysis program for participants with intensive PK sampling.

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Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	Area under the plasma concentration-time curve from time zero extrapolated to infinite time
Ctrough	Trough observed plasma concentration
T-Half	Terminal elimination half-life
CLT/F	Apparent clearance of drug after extravascular administration
Vz/F	Apparent volume of distribution of terminal phase

Blood samples (3 mL/sample) for oral azacitidine PK assessment will be collected from pre-dose to 6 hours after dose administration.

The study sites that can perform intensive PK sampling will perform intensive PK sampling at the time points indicated in Table 9.5-1.

Sparse PK sampling will be in the other participants who will not participate in intensive PK sampling at the time points indicated in Table 9.5-2.

Table 9.5-1: Intensive Pharmacokinetic Sampling Schedule for CC-486

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time Relative to CC-486 Dose (hr:min)[a]	CC-486 PK Plasma Sample
Cycle 1 Day 1	Predose	0:00	X
		0:30	X
		1:00	X
		1:30	X
		2:00	X
		2:30	X
		4:00	X
		6:00	X
Cycle 1 Day14	Predose	0:00	X
		0:30	X
		1:00	X
		1:30	X
		2:00	X

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Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time Relative to CC-486 Dose (hr:min)[a]	CC-486 PK Plasma Sample
		2:30	X
		4:00	X
		6:00	X

Abbreviations: hr, hours; min, minutes, PK, pharmacokinetic.

[a] Windows of PK sampling times are as follows: ≤ 60 minutes for predose PK samples; ± 5 minutes for 0.5, 1.0, 1.5, 2.0 and 2.5 hour PK samples; and ± 10 minutes for 4.0 and 6.0 hours PK samples.

Table 9.5-2: Sparse Pharmacokinetic Sampling Schedule for All Other Participants

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time Relative to CC-486 Dose (hr:min)	CC-486 PK Plasma Sample
Cycle 2 Day 1		0:30 to 6:00	X[a]
Cycle 2 Day 1		0:30 to 6:00	X[a]
Cycle 3 Day 1		0:30 to 6:00	X[a]
Cycle 3 Day 1		0:30 to 6:00	X[a]

Abbreviaations: hr, hours; min, minutes, PK, pharmacokinetic.

[a] PK samples to be collected between 0.5 and 6 hours at least 2 hours apart.

Placebo samples will not be analyzed.

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK samples.

Concentration analyses for azacitidine will be performed by validated bioanalytical method(s).

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, metabolite analyses, etc) and/or for additional method purposes (including, but not limited to, cross-validation cutpoint, etc).

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

9.6 Genetics

At screening and end of treatment, peripheral blood sampling for pharmacogenomic analysis is mandatory and participant 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.

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Refer to the Laboratory Manual for sample collection, handling, and processing instructions.

Other correlative assessments may include, but are not limited to, AML gene mutation sequencing and DNA methylation. Results from these studies will be evaluated in association with parameters of clinical benefit to determine whether biomarkers of response or non-response to treatment may be identified.

9.7 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in Table 9.7-1. The date and time of collection will be recorded in the source documents and eCRFs.

At baseline and post treatment, bone marrow aspirate (BMA) samples will be collected for assessing disease and response (ie, cytomorphology, cytogenetics, minimal residual disease). If adequate BMA is not obtainable, then a bone marrow biopsy should be completed.

Refer to the Laboratory Manual for sample collection, handling, and processing instructions.

Table 9.7-1: Biomarker Sampling Schedule (All Participants)

Study Day of Sample Collection (1 Cycle = 4 Weeks)[a]	Pharmacogenomic Blood Sample	Bone Marrow Aspirate (MRD)[b]	Biomarker Blood Assessment (PD)[c]	Biomarker Bone Marrow Assessment (NGS)[d]
Screening	X	X	X	X[d]
Cycle 1 Day 1			X	
Cycle 3 Day 1		X	X	
Cycle 6 Day 1		X		
Cycle 9 Day 1		X		
Cycle 12 Day 1		X		
Cycle 15 Day 1		X		
Cycle 18 Day 1		X		
Cycle 21 Day 1		X		
Cycle 24 Day 1		X		
Cycle 30 Day 1		X		
Cycle 36 Day 1		X		
EOT	X	X		

Abbreviations: DNA, deoxyribonucleic acid; EOT, end of treatment; IgG, immunoglobulin G; IgM, immunoglobulin M; MRD, minimal residual disease; NGS, next generation sequencing; PD, pharmacodynamic.

[a] All sample collection for biomarker assessments will be done predose at the selected time points.

[b] Suggested MRD time points to parallel clinical assessment.

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[c] Pharmacodynamics blood samples (for DNA methylation analyses) will be collected predose at the time points indicated.

[d] Targeted sequencing of AML-specific genes (gene panel) using NGS will be conducted on screening samples.

9.8 Additional Research

This protocol will include residual sample storage for additional research. Additional and optional research as described below may be performed using leftover samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

- Additional research related to the study intervention and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.
- Optional research not related to the study intervention or the participant's disease may be performed. The participant's decision to participate in this optional research will not impact his/her ability to participate in the main study.

For All sites:

Additional research is required for all study participants, except where prohibited by IRB/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

Additional research is intended to expand the R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

Residual blood and bone marrow samplings from biomarker collections (see Table 9.7-1) will also be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository in [redacted], or an independent, BMS-approved storage vendor.

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The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be participant to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

The primary endpoint is RFS. Based on the median RFS in the CC-486 and placebo groups of Study CC-486-AML-001, the expected median RFS was set at 4.8 months for placebo, and the expected median RFS was set at 9.5 months for CC-486.

As the primary efficacy analysis, a Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI for CC-486 relative to placebo. RFS curves will be estimated using Kaplan-Meier (KM) methods. The primary objective of this study is to estimate the efficacy of CC-486 as maintenance therapy by using RFS. The study does not plan to conduct any formal statistical hypothetical testing. For participants who do not have an RFS event, their RFS time will be censored at the last contact date (or "last known RFS date"). RFS will be censored at the date of randomization for participants who were randomized but had no response assessment.

Analysis of the primary endpoint will be conducted when the last subject completes 12 months follow-up. However, it may need to be reconsidered depending on the occurrence status of the event.

10.2 Sample Size Determination

The sample size is primarily calculated as approximately 15 based on the feasibility of enrollment taking into consideration of the anticipated difficulty to find candidates who have achieved CR/CRi with conventional intensive chemotherapy in Japan. However, as many participants as possible will be enrolled.

With a sample size of 15 participants, assuming 2:1 ratio to adequately secure the number of participants in CC-486 group and to keep the number in the placebo group to a minimum, then approximately 10 participants will receive CC-486, and approximately 5 participants will receive

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placebo. Based on this sample size, the probability that the point estimate of hazard ratio of CC-486 versus placebo becomes less than 1 is 87%).

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Intent-to-treat (ITT)	All participants who have agreed to participate in the study following completion of the informed consent process and registered into the IRT, regardless of whether they received treatment.
Modified intent-to-treat (mITT)	All participants who have met all inclusion/exclusion criteria and experienced no major protocol deviations during the study, and received a minimum of 1 cycle of treatment. Participants who are registered without confirmed CR/CRi per central review will be excluded from the mITT population.
Safety	All participants who received at least 1 dose of study intervention.
Pharmacokinetic (PK)	All participants who received at least 1 dose of study intervention and have measurable plasma concentration data. All analysis of PK data will be based on the PK population.
Health-related Quality of Life	All participants in the ITT Population with a valid health-related quality of life assessment at baseline and at least 1 valid post-baseline assessment.

Abbreviations: CR, complete remission, CRi, complete remission with incomplete blood count recovery; IRT, Interactive Response Technology; ITT, intent-to-treat; mITT, modified intent-to-treat; PK, pharmacokinetic.

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints. This section describes all of the planned analyses in this protocol but some of them may not necessarily provide statistically meaningful estimate due to the limited sample size. In such case, the best available summary and/or descriptive statistics will be provided.

A description of the participant population will be included in the clinical study report, including subgroups of age, gender, race, and other study-specific populations and demographic characteristics. A description of participant disposition will also be included in the clinical study report.

10.4.1 *General Considerations*

The primary and secondary estimands are described in Table 4-1.

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10.4.2 *Primary Endpoint(s)*

The primary efficacy endpoint of RFS is defined as the time from randomization to the date of documented relapse after CR or CRi per central review, or death from any cause, whichever occurs first. Participants 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.

The primary efficacy analysis will be conducted for the ITT Population and will compare the RFS distributions between the two treatment groups. A Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI for CC-486 relative to placebo. The RFS curves will be estimated for the primary efficacy endpoint, time to the date of documented relapse after CR or CRi or death from any cause, whichever occurs first, using Kaplan-Meier (KM) methods. Kaplan-Meier estimates for median RFS as well as the 25^{th} and 75^{th} percentiles and associated two-sided 95% CIs will be summarized for each treatment group. Plots of the KM survival curves will be presented for the two treatment groups.

Additionally, KM methods will be used to estimate the 1-year and 2-year RFS 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.

Additional sensitivity analyses, based on the mITT Population and the ITT Population, will be performed using modified RFS definitions. For these analyses of RFS, participants lost to follow-up without documented relapse will be 1) considered as having an event and 2) considered as having an event if they were randomized to the CC-486 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.

To assess and compare the modified definition of AML relapse being used in this protocol as a criterion 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, an exploratory analysis based on the mITT 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. Participants 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.

10.4.3 *Secondary Endpoint(s)*

Overall Survival

The secondary efficacy endpoint of OS is defined as the time from randomization to death from any cause and will be calculated using the randomization date and date of death, or date of last follow-up for censored participants. All participants will be followed until dropout, death, or study termination. Participants who dropout or are alive at study termination will have their OS times censored at the time of last contact, as appropriate. OS analysis will be conducted for the ITT population.

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Safety

All safety analyses will be performed on the Safety Population. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent adverse events (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 NCI-CTCAE (Version 5.0) 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.

Pharmacokinetics

The sparse concentration-time data collected in this study may be combined with a larger dataset to help further develop and validate the population pharmacokinetic model for azacitidine and to aid in the identification of covariates that influence azacitidine pharmacokinetic and/or pharmacodynamic measures and efficacy and safety endpoints. PK population will be used for PK analysis. Noncompartmental analysis will be performed using intensive sampling data.

Health-related Quality of Life

PRO endpoints include FACIT-Fatigue and the EQ-5D-5L, and analyses will include the Health-related Quality of Life population. Summary statistics (N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum) for PRO measures at each assessment point will be provided for each treatment arm. The mean change from baseline will also be reported at each post-baseline assessment point. Additionally, for the EQ-5D-5L, the proportion of participants endorsing each response option will be calculated at each time point.

Health utility scores as assessed by the EQ-5D-5L will be derived for each subject using country-specific weights (primary analysis will be done using UK weights). Using EQ-5D-5L scoring instructions, utility and VAS scores will be analyzed using the change from baseline assessment at each post-screening time point.

Additional details will be provided in the SAP.

10.4.4 *Exploratory Endpoint(s)*

Exploratory correlative analyses will be performed to assess the relationship between oral azacitidine concentration data and pharmacodynamic, safety, and efficacy endpoints. Appropriate analyses using population pharmacokinetic/pharmacodynamic approaches will be performed.

Complete cytogenetic remission (CRc) rate is defined according to the IWG AML response criteria. The CRc will be assessed in the subset of participants who have not achieved CRc at baseline.

For exploratory analyses, blood and bone marrow will be collected from participants from the time of diagnosis (if available), post induction and during maintenance therapy for molecular and/or cellular biomarker measurements. Results from DNA methylation and/or cytogenetics/gene mutation analyses will be evaluated in association with parameters of clinical outcome to

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determine whether biomarkers predictive of OS or RFS may be identified. The assays will be performed on participants in both treatment groups, placebo and CC-486. Thus a distinction between the prognostic and/or predictive nature of the marker(s) will be evaluated.

The relationship between genomic, molecular biomarkers and clinical outcomes will be assessed in participants with AML.

10.4.5 *Other Safety Analysis*

Not applicable.

10.4.6 *Other Analyses*

Other analyses may include analyses of assessments, which are not defined as endpoints, that need to be prespecified and not necessarily be reported in the clinical study report, such as, but not limited to, immunogenicity, biomarkers, population PK, and health technology assessment-related endpoints.

PK and biomarker exploratory analyses will be described in the SAP finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

10.5 Interim Analyses

Not applicable.

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12 APPENDICES

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APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leucemia
AST	aspartate transaminase
AxMP	auxiliary medicinal product
BM	bone marrow
BMS	Bristol-Myers Squibb
BSC	best supportive care
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CMML	chronic myelomonocytic leukemia
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
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
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
EOT	end of treatment
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
ESA	Erythropoiesis-stimulating agent
FAB	French-American-British
FACIT	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

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HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HR	hazard ratio
HRQoL	health-related quality-of-life
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICG	informed consent form
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	Investigational Medicinal Product
IP	investigational Product
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IWG	International Working Group
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	modified intent-to-treat
MRD	minimal residual disease
mRFS	median relapse-free survival
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
PR	partial remission
PS	performance status

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QD	once daily
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
RFS	relapse-free survival
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SCT	stem cell transplantation
SD	standard deviation
SUSAR	suspected, unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSA	thrombopoiesis-stimulating agent
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

Regulatory and Ethical Considerations

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

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- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, also by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC
- Regulatory authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, also by the local Health Authority, must be sent to Bristol-Myers Squibb (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with regulations, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

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The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA Authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

In situations where consent cannot be given by participants, their legally acceptable representatives (as per country regulation) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

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If informed consent is initially given by a participant's legally acceptable representative or legal guardian and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in the examples; hospital records; clinic and office charts; laboratory notes; memoranda; participant'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 eCRFs or CD-ROM.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

Study Intervention Records

Records must be made available for review at the request of BMS/designee or a Health Authority. Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

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If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include IP sourced from the sites' stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the

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electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the Sponsor or designee.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For eCRFs, review and approval/signature is completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

Each individual electronically signed eCRF must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

Monitoring

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor or designee.

Records Retention

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or its designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

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BMS or its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or its designee.

Return of Study Treatment

For this study, study treatments (those supplied by BMS or a vendor or sourced by the investigator), such as partially used study treatment containers, vials, and syringes, may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatment containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

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- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Study and Site Start and Closure

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Dissemination of Clinical Study Data

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases

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in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

Clinical Study Report

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- Participant recruitment (eg, among the top quartile of enrollers)

Scientific Publications

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the Clinical Trial Agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

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For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

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APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Adverse Events

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met.

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Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 for reporting pregnancies.)

Evaluating AEs and SAEs

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information for marketed products in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and grade the intensity of AEs and SAEs based upon the symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0)

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

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Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

Reporting of SAEs to Sponsor or Designee

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed facsimile transmission.

SAE Email Address: worldwide.safety@BMS.com

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

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APPENDIX 4 CONTRACEPTION REQUIREMENTS

Refer to Protocol Section 6.1, Inclusion Criteria, for contraception time frames.

Methods of Contraception

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly*[a]
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by Women of childbearing potential (WOCBP) participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Oral (birth control pills) • Intravaginal (rings) • Transdermal Combined (estrogen and progestogen-containing) hormonal contraception must begin at least 28 days prior to initiation of study therapy.
Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] Oral Injectable Progestogen-only hormonal contraception must begin at least 28 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] Intrauterine device. Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b, c] Bilateral tubal occlusion.

Vasectomized partner

Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.

Sexual abstinence

- Sexual abstinence is considered a highly effective method only if defined as absolutely (100% of time) refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study. For abstinence to be considered an acceptable method of contraception, it must be the preferred and usual lifestyle of the study participant.

Continuous abstinence must begin at least 28 days prior to initiation of study therapy.

It is not necessary to use any other method of contraception when complete abstinence is elected.

WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in the protocol Schedule of Activities (Section 2).

Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the investigational product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Collection of Pregnancy Information

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and APPENDIX 3.

APPENDIX 5 ECOG PERFORMANCE STATUS CRITERIA

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, 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: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

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APPENDIX 6 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: Cheson BD, Bennett JM, Kopecky KJ, et al. Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.

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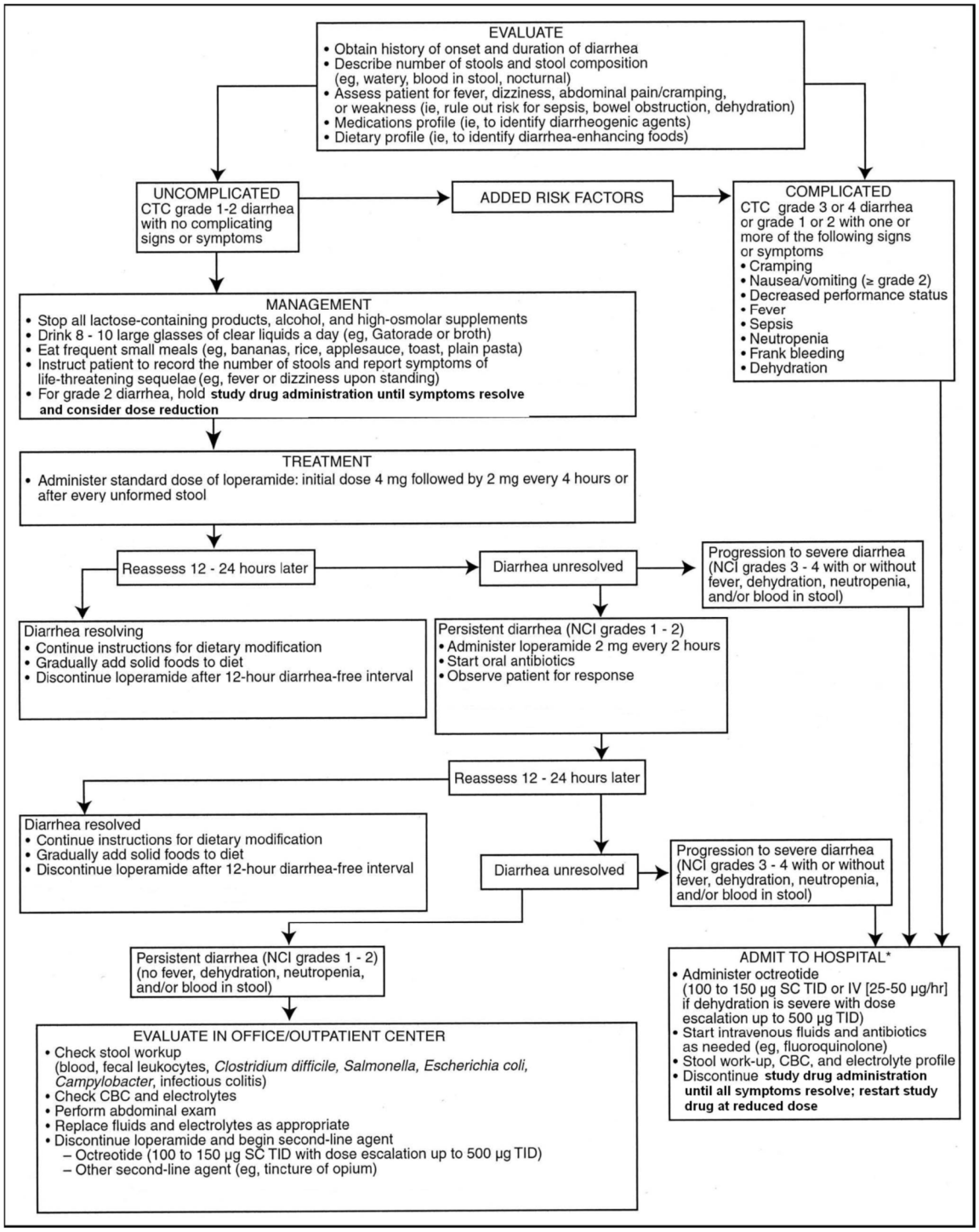
APPENDIX 7 RECOMMENDATIONS FOR MANAGEMENT OF TREATMENT-INDUCED DIARRHEA

The following published guidelines (Benson, 2004) were modified in order to be consistent with the clinical study protocol.



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APPENDIX 8 FACIT-FATIGUE SCALE (VERSION 4)

Below is a list of statements that other people with your illness have said are important.

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

		Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

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APPENDIX 9 EQ-5D-5L HEALTH QUESTIONNAIRES

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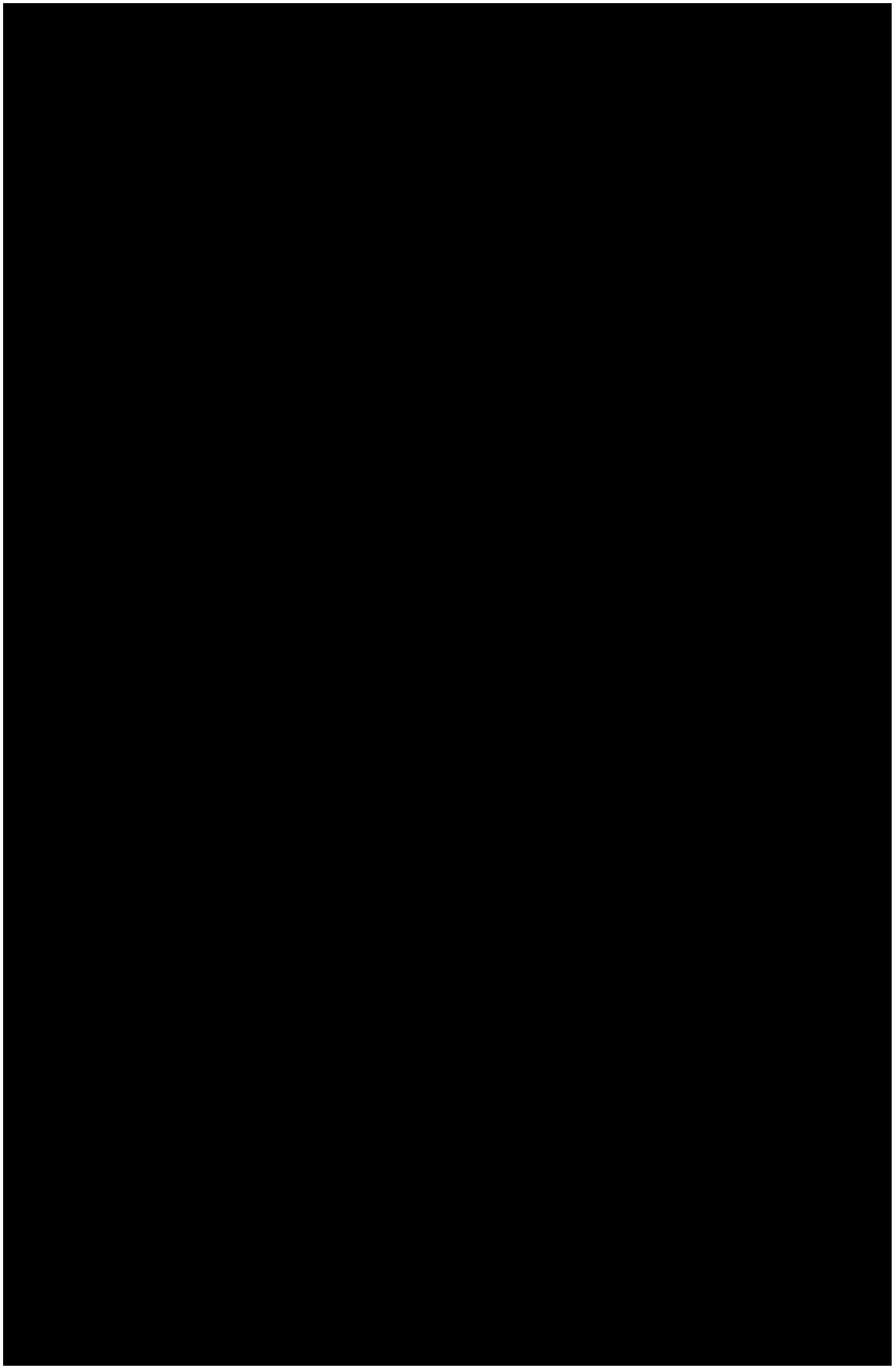

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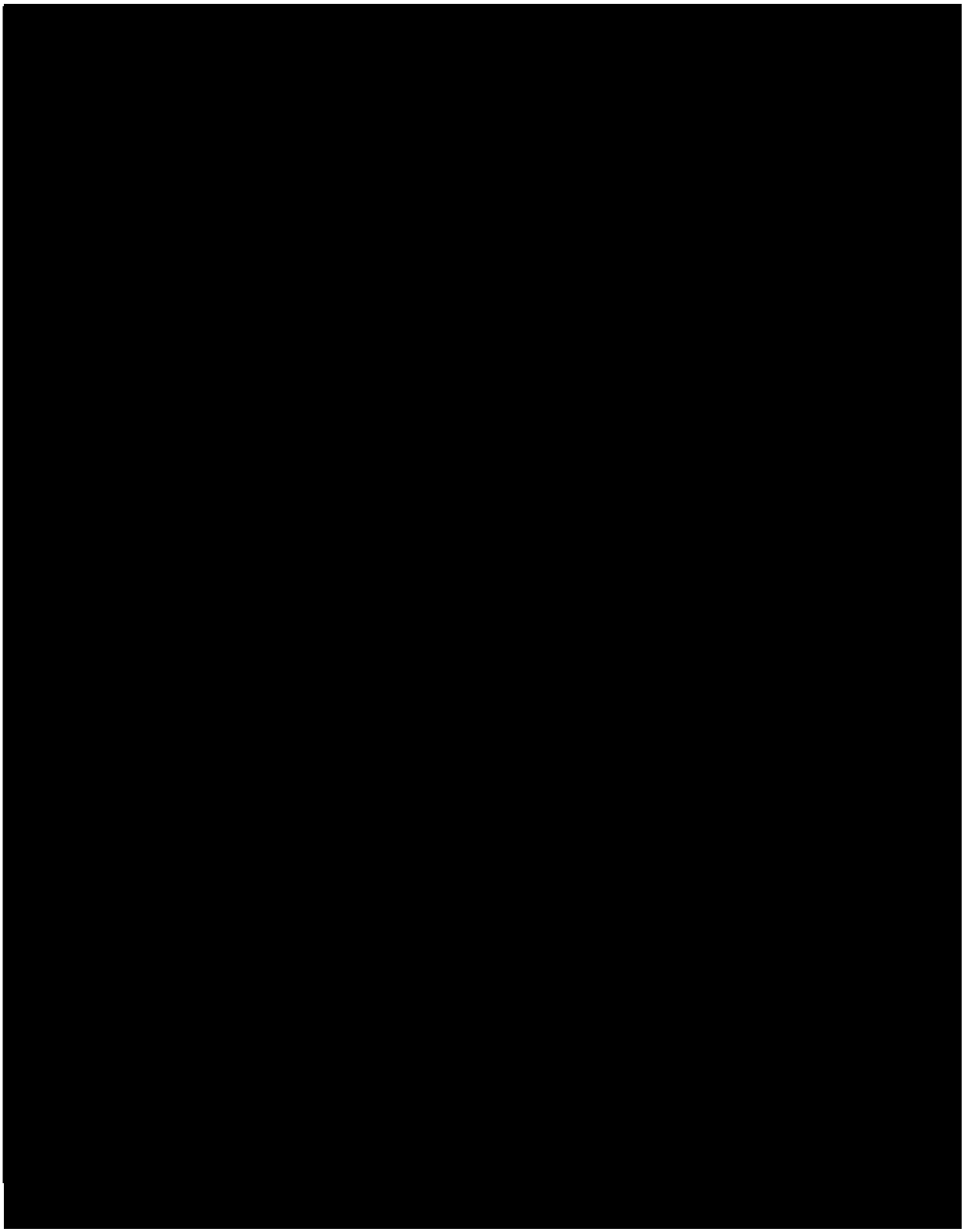

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APPENDIX 10 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 01, 25-July-2022

The main objective of Protocol Amendment 01 is to add an Eastern Cooperative Oncology Group (ECOG) performance status as a new inclusion criterion. Additionally, updates were made to clarify the assessments to be performed at appropriate time points, improve alignment across protocol sections and establish consistency, and update contact information.

Other revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Updated contact information for the Clinical Trial Physician and Clinical Scientist as well as Bristol Myers Squibb KK headquarters relocation.	Sponsor contract information was updated.
Protocol Summary Section 3.1: Study Rationale Section 3.2: Background	The dose of daunorubicin for common induction regimen was aligned with the National Comprehensive Cancer Network (NCCN) guideline.	The dose of daunorubicin was modified to align with the NCCN guideline.
Table 2-1: Screening Procedural Outline (CA055005)	ECOG Performance Status was updated to perform the evaluation at randomization or Cycle 1 Day 1 (C1D1).	Table was updated to perform the assessment at the appropriate time point.
Table 2-3: End-of-treatment and Follow-up Procedural Outline (CA055005)	Concomitant Medications, Therapy and Procedures was updated to include assessments at End of Treatment/Early Termination and Follow-up.	Table was updated to perform the assessment at the appropriate time point.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1 Inclusion Criteria	Modified inclusion criterion 2) b); Must have achieved first complete remission (CR)/complete remission with incomplete blood count recovery (CRi) status within 4 months (± 7 days) prior to "randomization", as evidenced by the following. Added a new inclusion criterion for ECOG performance status.	The 4 month duration prior to randomization for first CR/CRi status was aligned with the protocol. Inclusion criterion was added to define the ECOG performance status.
Section 7.3 Blinding	Removed the description of randomization schedules.	This process is not applied to this study.
Section 9.5 Pharmacokinetics	Modified the descriptions and added the definition of pharmacokinetic parameters.	The descriptions were modified based on BMS formatting.
Table 9.7-1: Biomarker Sampling Schedule (All Participants)	Removed Biomarker Bone Marrow Assessment (NGS) at Diagnosis. Removed Bone Marrow Aspirate (MRD) at Cycle 1 Day 1.	No sample collection for NGS or MRD occurs at Diagnosis and Cycle 1 Day 1.
Appendix 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING	Assessment of Intensity was updated to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 grading.	The severity was aligned with Section 7.4.1: Dose Modifications for Toxicity.

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