Official Title of Study:

A Phase 3, Multicenter, Open-label, Randomized Study Comparing the Efficacy and Safety of AG-221 (CC-90007) Versus Conventional Care Regimens in Older Subjects with Late Stage Acute Myeloid Leukemia Harboring an Isocitrate Dehydrogenase 2 Mutation

PROTOCOL(S) AG-221-AML-004

NCT Number: NCT02577406

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A PHASE 3, MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY COMPARING THE EFFICACY AND SAFETY OF AG-221 (CC-90007) VERSUS CONVENTIONAL CARE REGIMENS IN OLDER SUBJECTS WITH LATE STAGE ACUTE MYELOID LEUKEMIA HARBORING AN ISOCITRATE DEHYDROGENASE 2 MUTATION

The "IDHENTIFY" Trial

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EudraCT NUMBER:	**2015-000344-42**
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SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Open-label, Randomized Study Comparing the Efficacy and Safety of AG-221 (CC-90007) Versus Conventional Care Regimens in Older Subjects with Late Stage Acute Myeloid Leukemia Harboring an Isocitrate Dehydrogenase 2 Mutation.

Indication

Treatment of subjects 60 years or older with acute myeloid leukemia (AML) refractory to or relapsed after second- or third-line AML therapy and positive for an isocitrate dehydrogenase 2 (IDH2) mutation

[redacted]

[redacted]

Objectives

Primary

- To determine the primary efficacy, measured as overall survival (OS), of AG-221 compared with conventional care regimens (CCRs) in subjects 60 years or older with AML refractory to or relapsed after second- or third-line AML therapy and positive for an IDH2 mutation

Secondary

- To determine the supporting efficacy of AG-221 compared with CCRs
- To determine the safety and tolerability of AG-221 compared with CCRs
- To determine the effect of AG-221 compared with CCRs on Health-related Quality-of-Life (HRQoL)

Study Design

This is an international, multicenter, open-label, randomized, Phase 3 study comparing the efficacy and safety of AG-221 versus CCRs in subjects 60 years or older with AML refractory to or relapsed after second- or third-line AML therapy and positive for an IDH2 mutation.

Screening procedures are to occur within 28 days prior to the start of study treatment and after the informed consent form (ICF) is signed. Diagnosis of AML disease and AML disease status at screening will be based on local review of pathology and cytogenetics. Positivity of IDH2 gene mutation in bone marrow aspirate and/or peripheral blood will be confirmed centrally at screening. (Note: in the event that the central laboratory result is delayed and precludes acute clinical management of a subject who has confirmed IDH2 gene mutation by local evaluation, the subject may be eligible for randomization with approval by the Medical Monitor.)

Following review of eligibility, subjects will be assigned by the investigator to one of the CCR treatment options based on the investigator's assessment of subjects' eligibility. The CCR treatment options include best supportive care (BSC) only, azacitidine subcutaneously (SC) plus BSC, low-dose cytarabine (LDAC) SC plus BSC, or intermediate-dose cytarabine (IDAC) intravenously (IV) plus BSC. The CCR treatment option chosen and the reason(s) for selecting the CCR treatment option will be recorded for all subjects prior to randomization.

Following the selection of a CCR treatment option, subjects will be randomized centrally in a 1:1 ratio to receive either the AG-221 treatment or the CCR treatment option pre-selected by the investigator. Randomization will be stratified by prior intensive therapy for AML (yes versus no), primary refractory (ie, morphologic complete remission [CR], CR with incomplete

neutrophil recovery [CRi] or CR with incomplete platelet recovery [CRp] has never been attained) (yes versus no), and prior allogeneic hematopoietic stem cell transplantation (HSCT) for AML (yes versus no).

Study treatment starts within 3 days after randomization. No crossover between any of the treatment options, including the CCR treatment options, will be permitted during the course of study treatment.

Assessments during study treatment include efficacy, safety, HRQoL, [redacted]

A retrospective central review of all bone marrow aspirates and/or biopsies, peripheral blood smears and cytogenetics collected during the study will be conducted by personnel blinded to subject treatment. The central assessments will be used in the statistical analyses. Disagreement between central and local assessments will be adjudicated by a third party reviewer and the adjudicated assessment will be used in the statistical analyses.

Response to treatment and hematologic improvement (HI) will be assessed by the investigators and retrospectively by a blinded Independent Response Assessment Committee (IRAC) according to modified International Working Group (IWG) AML Response Criteria (Appendix F) and IWG myelodysplastic syndromes HI criteria (Appendix H), respectively.

Dosing interruptions, dosing delays or dose modifications may occur for managing toxicities and/or augmenting treatment response during study treatment (refer to Section 7.2).

Subjects can continue to receive study treatment provided that they benefit from study treatment and all protocol-specified criteria for continuing study treatment are met. Study treatment will be discontinued if the investigator has alternative therapies (eg, HSCT) and/or considers study treatment to be no longer beneficial to the subject, or the rapidity of change of disease state renders it unacceptable for further study treatment in the judgment of the investigator. Refer to Section 11.1 for sufficient reasons for discontinuing a subject from study treatment.

The decision to discontinue a subject, which will not be delayed or refused by the Sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

All subjects who have received at least one dose of study treatment should undergo end of treatment (EOT) evaluations (Section 6.2.3) when study treatment is discontinued. The reason for discontinuation will be recorded in the electronic case report form (eCRF) pages and in the source document.

All subjects discontinued from study treatment for any reason other than withdrawal of consent for follow-up will continue to be assessed for adverse events (AEs), concomitant medications, concomitant procedures, transfusions, [redacted] response, hematologic improvement, subsequent AML therapies and survival. Refer to Section 6.3 for details regarding the assessments scheduled after the EOT visit.

The study will be conducted in compliance with International Council on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

This study will enroll 316 subjects 60 years or older with AML refractory to or relapsed after second- or third-line AML therapy and positive for an IDH2 mutation.

Length of Study

The expected duration of this study is approximately 78 months, including an enrollment period of approximately 42 months, followed by approximately 7 months of treatment and/or posttreatment follow-up to reach the total number of events (see below Statistical Methods Section and Section 9) required for a fully-powered analysis of OS.

The End of Trial is defined as either the date of 36 months from the last subject randomized date, or the date when all subjects discontinued from study treatment and no subject is available for survival follow-up, whichever is the later date.

Study Treatments

The options in the CCR treatment arm include:

- BSC only: continuous 28-day cycles of BSC. Best supportive care includes, but is not limited to, hydroxyurea for leukocytosis and/or differentiation syndrome associated with therapy of mutant IDH inhibition (ie, IDH differentiation syndrome), anti-infectives, analgesics, antiemetics, antipyretics, transfusions and nutritional support (refer to Section 7.1.5 and Section 8 for details);
- Azacitidine SC plus BSC: continuous 28-day cycles of azacitidine 75 mg/m^2/day SC for 7 days, plus BSC;
- LDAC SC plus BSC: continuous 28-day cycles of cytarabine 20 mg SC twice a day (BID) for 10 days, plus BSC;
- IDAC IV plus BSC: 28-day cycles of cytarabine 0.5 to 1.5 g/m^2/day IV for 3 to 6 days, per standard institutional practice, plus BSC; only BSC given after IDAC therapy concludes per standard institutional practice. (Note: any local standard regimen different from the above specification will need review and approval by the Medical Monitor.)

Subjects randomized to the AG-221 treatment arm will receive continuous 28-day cycles of AG-221 100 mg orally (PO) once a day (QD) for 28 days, plus BSC. Dose escalation to 200 mg may occur for augmenting treatment response (detailed in Section 7.2.1.2).

Study treatments as described above can continue until the End of Trial, unless discontinued for any of the reasons detailed in Section 11.1.

Overview of Key Efficacy Assessments

The primary efficacy endpoint is OS.

The key secondary efficacy endpoints include overall response rate and event-free survival. Response will be assessed retrospectively by a blinded IRAC through collection of central hematology parameters, central assessments of bone marrow aspirates and/or biopsies, peripheral blood smears and cytogenetics, and results of other pertinent tests.

Overview of Key Safety Assessments

Safety assessments include physical examination, vital signs, electrocardiogram, hematology, serum chemistry, cardiac markers, fasting (preferred) lipid panel, pregnancy testing (for females of childbearing potential only), AEs, concomitant medications, concomitant procedures and transfusions. After screening, echocardiogram, urinalysis and coagulation will be repeated as clinically indicated.

Statistical Methods

The primary efficacy endpoint of OS is defined as time from randomization to death due to any cause. The equality of overall survival cures will be compared between the AG-221 and CCR treatment arms using a stratified log-rank test. Assuming a median OS of 5.6 months in the CCR treatment arm (Roboz, 2014), a median OS of 8 months in the AG-221 treatment arm (42.9% improvement), and a drop-out rate of approximately 9%, this design requires 250 deaths and 316 subjects (158 per treatment arm) to be randomized in order to achieve 80% power to detect a constant hazard ratio of 0.7 and demonstrate a statistically significant difference in OS at a Type I error rate of 0.05 (two-sided). An interim analysis for superiority will be conducted at 65% information (ie, 163 deaths) based on Lan-DeMets version of the O'Brien-Fleming alpha spending function.

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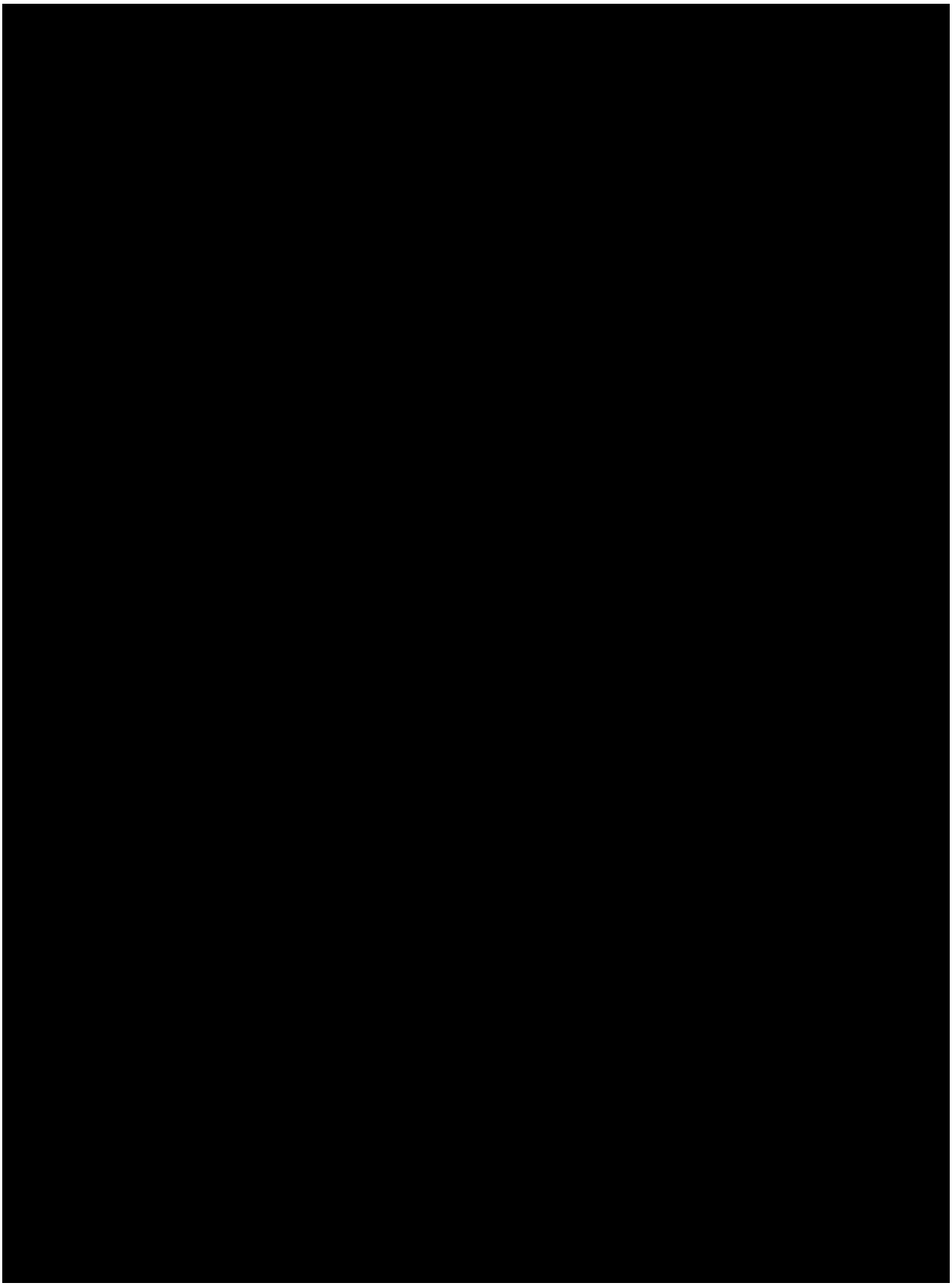

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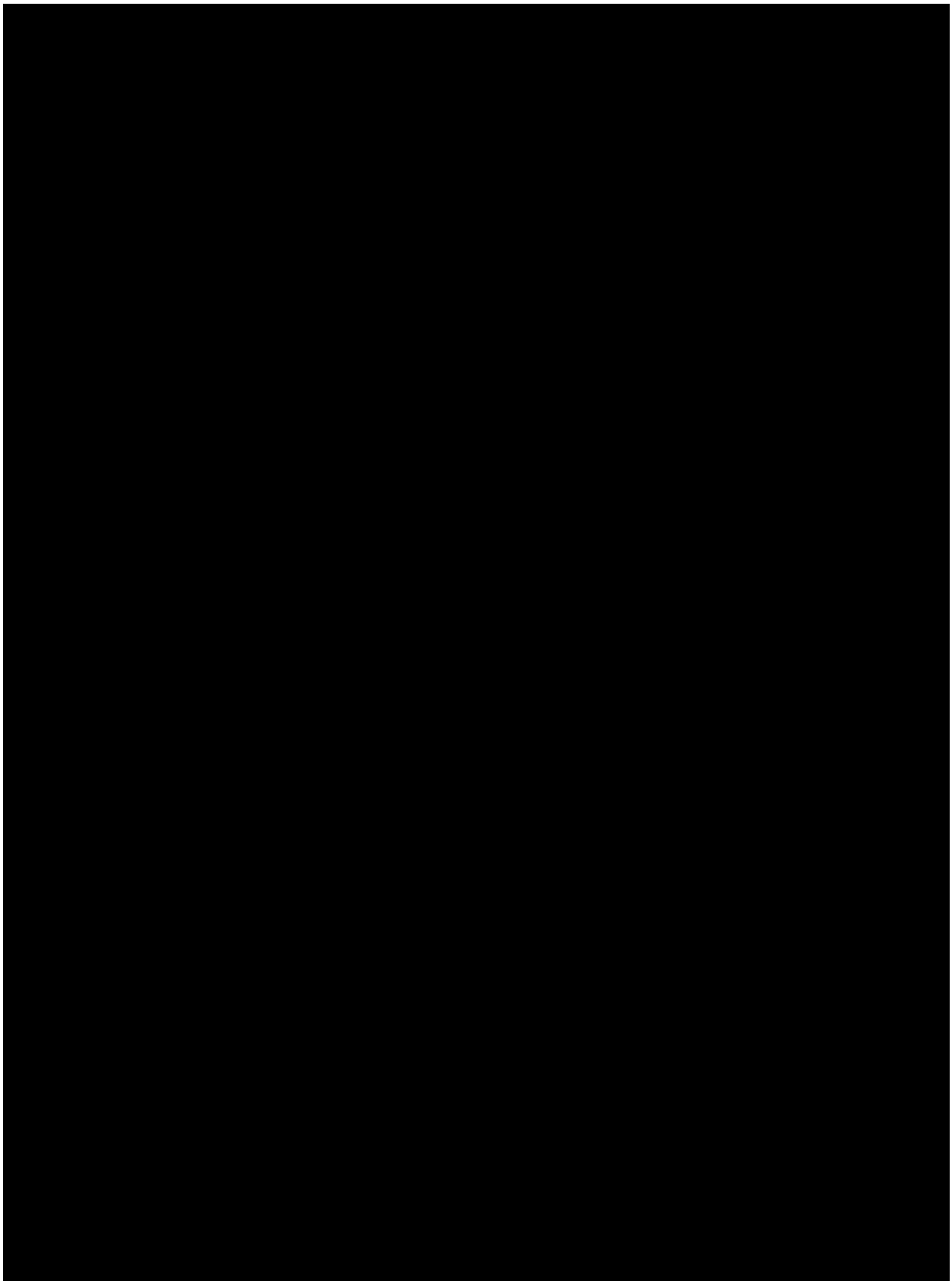

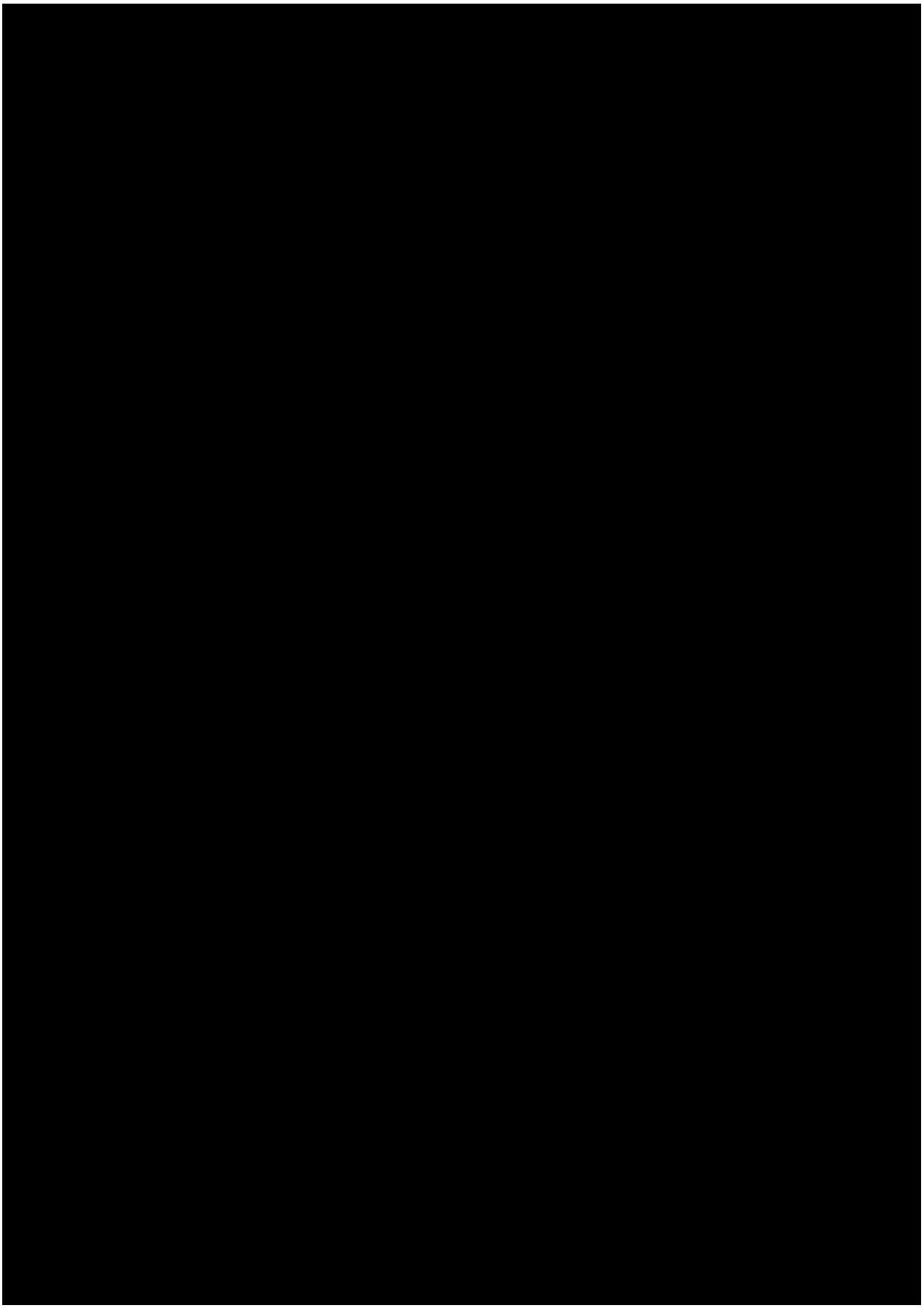

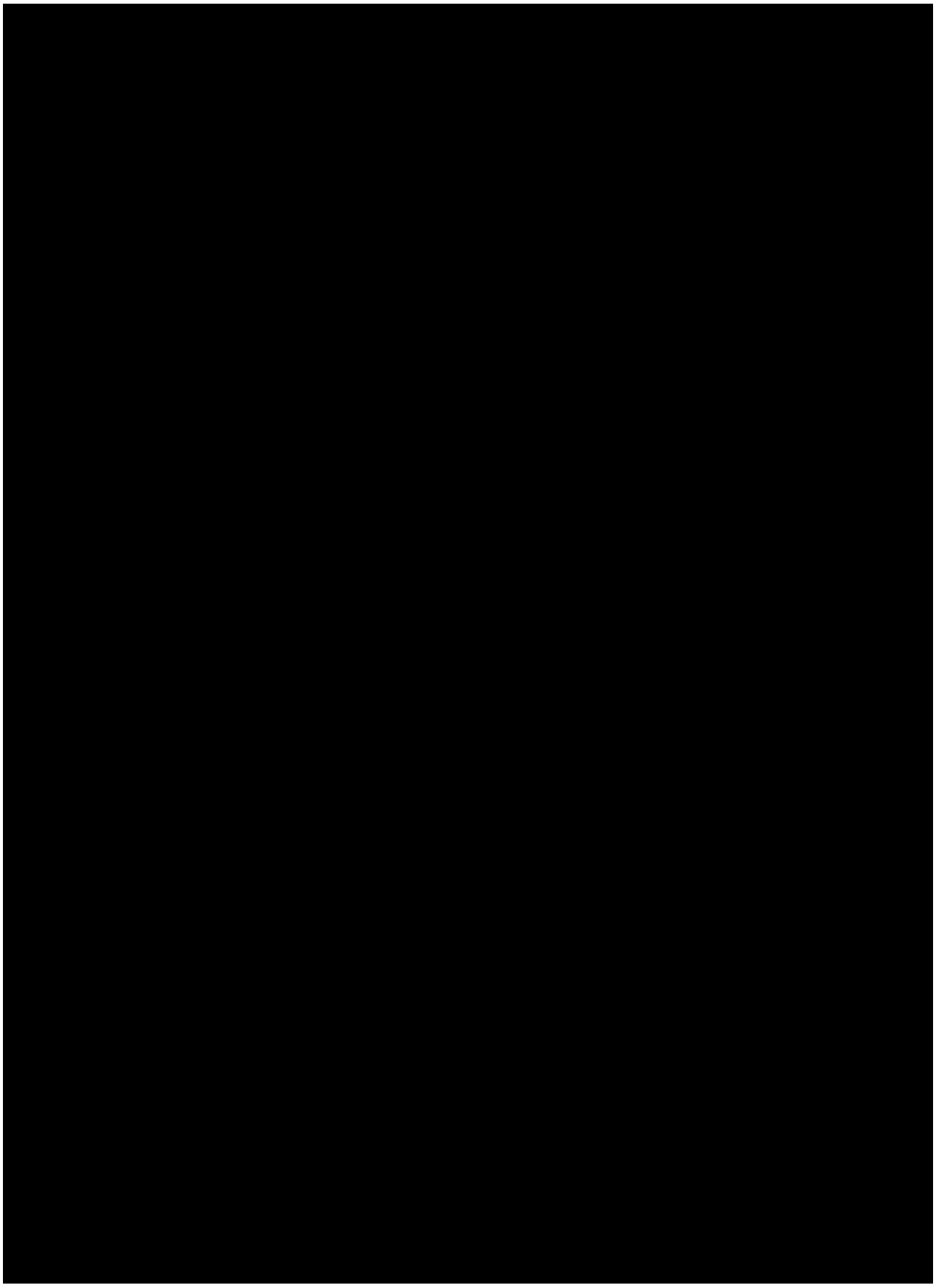

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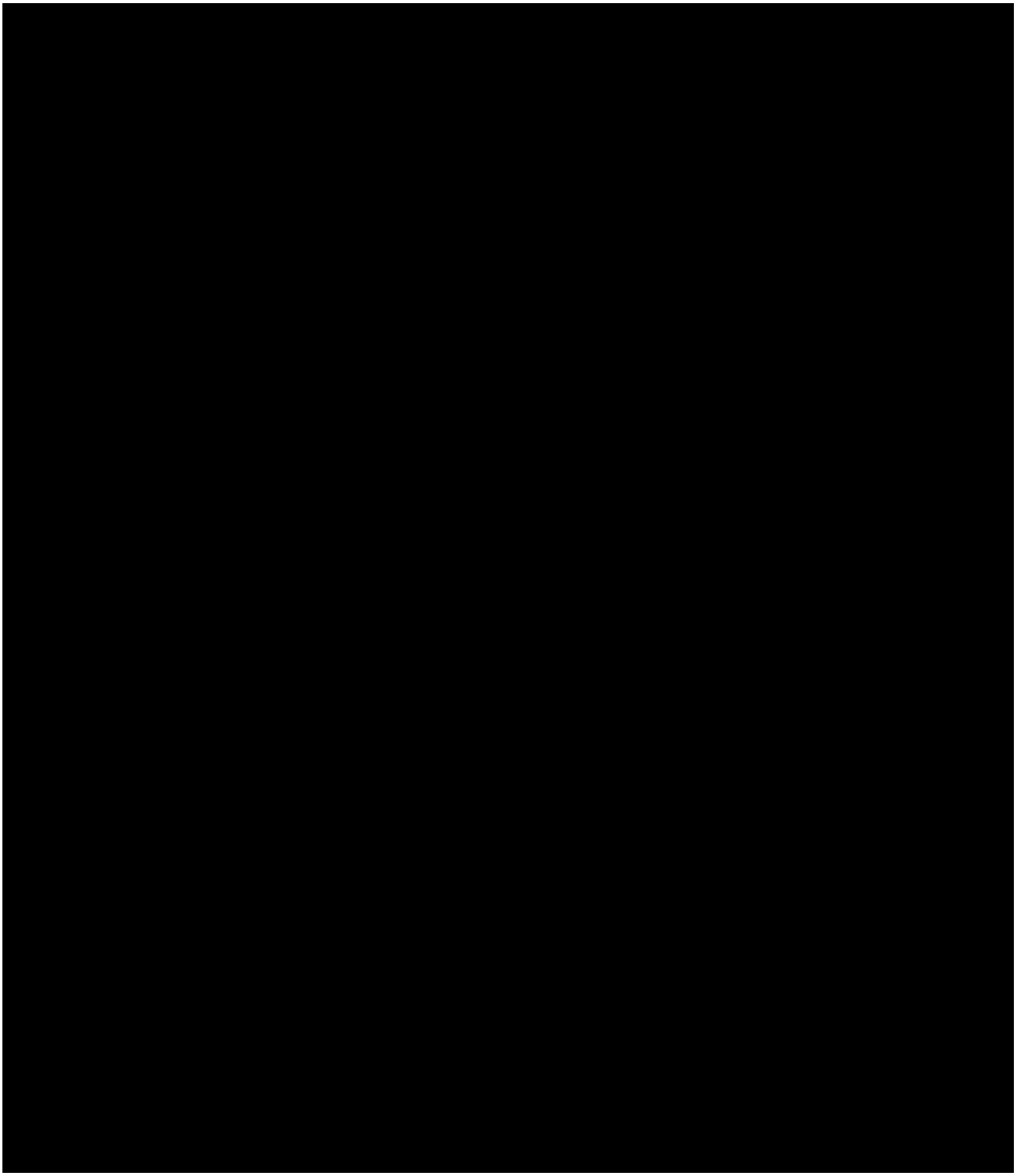


2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is • To determine the primary efficacy, measured as overall survival (OS), of AG-221 compared with conventional care regimens (CCRs) in subjects 60 years or older with AML refractory to or relapsed after second- or third-line AML therapy and positive for an IDH2 mutation
Secondary Objective(s)
The secondary objectives are • To determine the supporting efficacy of AG-221 compared with CCRs • To determine the safety and tolerability of AG-221 compared with CCRs • To determine the effect of AG-221 compared with CCRs on Health-related Quality-of-Life
[redacted]

Table 2: Study Endpoints

Endpoint	**Name**	**Description**	**Timeframe**
Primary	Overall survival	Time from randomization to death due to any cause	Up to ~ 49 months
Secondary	Overall response rate	Rate of MLFS + CR + CRi + CRp + PR according to modified IWG AML response criteria (Appendix F)	Up to ~ 49 months
		Rate of CR/CRh (assessed by the Sponsor only and based on laboratory dataset; Appendix F).	Up to ~ 49 months
	Event-free survival	Time from randomization to documented morphologic relapse, PD according to modified IWG AML response criteria (Appendix F) or death from any cause, whichever occurs first	Up to ~ 49 months

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary (continued)	Duration of response	Time from the first documented MLFS/CR/CRi/CRp/PR to documented morphologic relapse, PD according to modified IWG AML response criteria (Appendix F) or death due to any cause, whichever occurs first	Up to ~ 49 months
		Time from the first documented CR/CRh to documented morphologic relapse, PD according to modified IWG AML response criteria (Appendix F) or death from any cause, whichever occurs first	Up to ~ 49 months
	Time to response	Time from randomization to first documented MLFS/CR/CRi/CRp/PR according to modified IWG AML response criteria (Appendix F)	Up to ~ 49 months
		Time from randomization to first documented CR/CRh (Appendix F)	Up to ~ 49 months
	Treatment mortality at 30 and 60 days	Rate of death from any cause within 30 and 60 days of initiation of study treatment	At 30 and 60 days after treatment start
	One-year survival	The probability of survival at 1 year from randomization	Up to ~ 49 months
	Overall remission rate	Rate of CR + CRi + CRp according to modified IWG AML response criteria (Appendix F)	Up to ~ 49 months
	Complete remission rate	Rate of CR according to modified IWG AML response criteria (Appendix F)	Up to ~ 49 months
	Hematologic improvement rate	Rate of HI-N + HI-P + HI-E according to IWG MDS HI criteria (Appendix H)	Up to ~ 49 months
	Rate of HSCT	Rate of bridge-to-HSCT through study treatment	Up to ~ 49 months
	Time to treatment failure	Time from randomization to discontinuation of study treatment due to any cause	Up to ~ 49 months
	Safety and tolerability	Type, frequency, severity, seriousness and relationship of adverse events to study treatments; vital signs; ECG; clinical laboratory evaluations	Up to ~ 78 months

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary (continued)	HRQoL	European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC QLQ-C30) (Appendix I) and EuroQoL Group EQ-5D-5L instrument (Appendix J)	Up to ~ 49 months
[redacted]			

Abbreviations: AML = acute myeloid leukemia; CR = morphologic complete remission; CRh = morphologic complete remission with partial hematologic recovery; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; ECG = electrocardiogram; EORTC= European Organization for Research and Treatment of Cancer; [redacted] HI = hematologic improvement; HI-E = hematologic improvement erythroid response; HI-N = hematologic improvement neutrophil response; HI-P = hematologic improvement platelet response; HRQoL = Health-related Quality of Life; HSCT = hematopoietic stem cell transplantation; IWG = International Working Group; MDS = myelodysplastic syndromes; MLFS = morphologic leukemia-free state; [redacted] PR = partial remission; PD = progressive disease.

3. OVERALL STUDY DESIGN

3.1. Study Design

This is an international, multicenter, open-label, randomized, Phase 3 study comparing the efficacy and safety of AG-221 versus CCRs in subjects 60 years or older with AML refractory to or relapsed after second- or third-line AML therapy and positive for an IDH2 mutation.

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

The study consists of a Screening Phase, a Treatment Phase and a Follow-up Phase.

Figure 1 provides a schematic of the overall study design.

3.1.1. Screening Phase

Screening procedures are to occur during the Screening Phase within 28 days prior to the start of study treatment and after the informed consent form (ICF) is signed.

Diagnosis of AML disease according to World Health Organization (WHO) classification (Appendix B) and AML disease status at screening according to modified International Working Group (IWG) AML Response Criteria (Appendix F) will be based on local review of pathology and cytogenetics.

A retrospective central review of screening bone marrow aspirates and/or biopsies, peripheral blood smears and cytogenetics will be conducted by personnel blinded to study treatment. The central cytogenetic review will provide standardized analysis and reporting for all subjects, regardless of the laboratory performing the initial analysis (local or central; Section 6.1). The central assessments will be used to confirm AML disease status at screening. If the central and local reviews disagree on AML disease status of a subject at screening, a third party reviewer will adjudicate and make the final assessment. If the subject was centrally confirmed to be ineligible for the study, the subject will be allowed to remain in the study, but will be excluded from the modified intent-to-treat (mITT) population (Section 9.2.2). Instructions for submission slides of bone marrow aspirate (and/or biopsy) and peripheral blood smear, and pertinent reports to central review are provided in the Study Reference Manual and Study Central Laboratory Manual.

Positivity of IDH2 gene mutation in bone marrow aspirate and/or peripheral blood will be confirmed centrally at screening. (Note: in the event that the central laboratory result is delayed and precludes acute clinical management of a subject who has confirmed IDH2 gene mutation by local evaluation, the subject may be eligible for randomization with approval by the Medical Monitor.)

Following review of eligibility, subjects will be assigned by the investigator to one of the CCR treatment options based on the investigator's assessment of subjects' eligibility. The CCR treatment options include best supportive care (BSC) only, azacitidine SC plus BSC, LDAC SC plus BSC, or IDAC IV plus BSC:

- BSC only: continuous 28-day cycles of BSC. Best supportive care includes, but is not limited to, hydroxyurea for leukocytosis and/or differentiation syndrome associated with therapy of mutant IDH inhibition (ie, IDH Differentiation Syndrome), anti-infectives, analgesics, antiemetics, antipyretics, transfusions and nutritional support (refer to Section 7.1.5 and Section 8 for details);
- Azacitidine SC plus BSC: continuous 28-day cycles of azacitidine 75 mg/m^2/day SC for 7 days, plus BSC;
- LDAC SC plus BSC: continuous 28-day cycles of cytarabine 20 mg SC BID for 10 days, plus BSC;
- IDAC IV plus BSC: 28-day cycles of cytarabine 0.5 to 1.5 g/m^2/day IV for 3 to 6 days, per standard institutional practice, plus BSC; only BSC given after IDAC therapy concludes per standard institutional practice. (Note: any local standard regimen different from the above specification will need review and approval by the Medical Monitor.)

The CCR treatment option chosen and the reason(s) for selecting the CCR treatment option will be recorded for all subjects prior to randomization.

Following the selection of a CCR treatment option, subjects will be randomized centrally in a 1:1 ratio to receive either the AG-221 treatment or the CCR treatment option pre-selected by the investigator. Randomization will be stratified by prior intensive therapy for AML (yes versus no), primary refractory (ie, CR, CRi or CRp has never been attained) (yes versus no), and prior allogeneic HSCT for AML (yes versus no).

Approximately 316 eligible subjects will be enrolled with 158 subjects per treatment arm.

3.1.2. Treatment Phase

Study treatment starts within 3 days after randomization. No crossover between any of the treatment options, including the CCR treatment options, will be permitted during the course of study treatment.

Assessments during study treatment include efficacy, safety, Health-related Quality-of-Life (HRQoL) questionnaires, [redacted].

A retrospective central review of all bone marrow aspirates and/or biopsies, peripheral blood smears and cytogenetics collected after the start of study treatment will be conducted by personnel blinded to subject treatment. The central cytogenetic review will provide standardized analysis and reporting for all subjects, regardless of the laboratory performing the initial analysis (local or central). The central assessments will be used in the statistical analyses. Disagreement between central and local assessments will be adjudicated by a third party reviewer and the adjudicated assessment will be used in the statistical analyses. Instructions for submission slides of bone marrow aspirate (and/or biopsy) and peripheral blood smear, and pertinent reports to central review are provided in the Study Reference Manual and Study Central Laboratory Manual.

Response to treatment and hematological improvement (HI) will be assessed by the investigators and by a blinded Independent Response Assessment Committee (IRAC) according to modified IWG AML Response Criteria (Appendix F) and IWG myelodysplastic syndromes (MDS) HI criteria (Appendix H), respectively.

Dosing interruptions, dosing delays or dose modifications may occur for managing toxicities and/or augmenting treatment response during study treatment (refer to Section 7.2 for details).

Subjects can continue to receive study treatment provided that they benefit from study treatment and all protocol-specified criteria for continuing study treatment are met. Study treatment will be discontinued if the investigator has alternative therapies (eg, HSCT) and/or considers the study treatment to be no longer beneficial to the subject, or the rapidity of change of disease state renders it unacceptable for further study treatment in the judgment of the investigator. Study treatment will be discontinued if females of childbearing potential (FCBPs) become pregnant during the study. Refer to Section 11 for events that are considered sufficient reasons for discontinuing a subject from study treatment.

The decision to discontinue a subject, which will not be delayed or refused by the Sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

All subjects who have received at least one dose of study treatment should undergo end of treatment (EOT) evaluations (Section 6.2.3) when study treatment is discontinued. The reason for discontinuation will be recorded in the electronic case report form (eCRF) pages and in the source document.

3.1.3. Follow-up Phase

All subjects discontinued from study treatment for any reason other than withdrawal of consent for follow-up will continue to be assessed for AEs, concomitant medications, concomitant procedures, transfusions, [redacted] response, hematologic improvement, subsequent AML therapies and survival. Refer to Section 6.3 for details regarding the assessments scheduled after the EOT visit. Females of childbearing potential should avoid becoming pregnant for 4 months after the last study treatment (6 months after the last dose of cytarabine), and male subjects and their partners should avoid conception for 4 months after the last study treatment (6 months after the last dose of cytarabine; 6 months after the last dose of azacitidine in Canada).

3.1.4. Interim Analysis

The study will have one interim analysis for superiority (Section 9.8). The interim efficacy analysis will be performed by an external independent third party and the results will be kept strictly confidential in order to maintain the integrity of the study. The interim results will be provided to an independent Data Monitoring Committee (DMC) who will review and give advice to the Sponsor regarding the study conduct. The analysis results will not be disseminated among investigators and those directly involved with the study conduct.

3.1.5. Data Monitoring Committee

An external independent unblinded DMC with multi-disciplinary representation will evaluate safety and interim efficacy in compliance with a prospective charter which contains the details of the DMC responsibilities, authorities and procedures.

3.2. Study Duration for Subjects

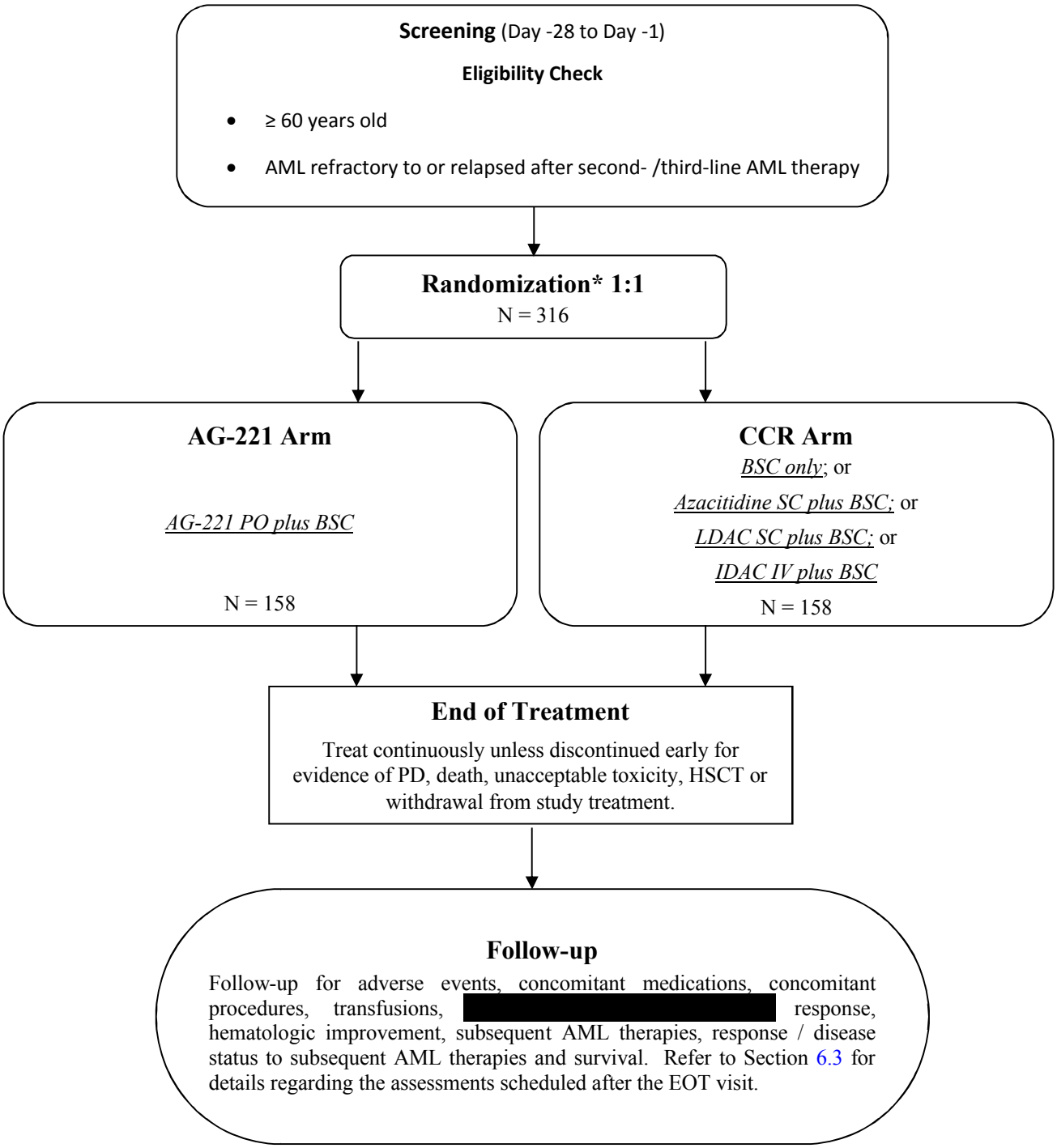
Study participation for each subject is approximately up to 78 months, an enrollment period of approximately 42 months including a screening period for up to 28 days, followed by approximately 7 months of treatment and/or posttreatment follow-up to reach the total number of events (see Section Section 9) required for a fully-powered analysis of OS.

3.3. End of Trial

The End of Trial is defined as either the date of 36 months from the last subject randomized date, or the date when all subjects discontinued from study treatment and no subject is available for survival follow-up, whichever is the later date.

The Sponsor may consider closing the trial when data supporting key endpoints and objectives of the study have been analyzed, and the availability of a roll-over or extension protocol exists into which any subjects who remain on study treatment may be consented and continue to receive access to study treatment. Such a protocol would be written for a compound that would not yet be commercially available.

Figure 1: Overall Study Design



Key: AML = acute myeloid leukemia; BSC = best supportive care; CCR = conventional care regimen; CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; EOT = end of treatment; HSCT = hematopoietic stem cell transplantation; IDAC = intermediate-dose cytarabine; IDH2 = isocitrate dehydrogenase isoform 2; IV = intravenously; LDAC = low-dose cytarabine; PD = progressive disease; PO = orally; SC = subcutaneously.

* Stratification factors: prior intensive therapy for AML (yes versus no), primary refractory (yes versus no), and prior allogeneic HSCT for AML (yes versus no).

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 316 subjects 60 years or older with AML refractory to or relapsed after second- or third-line AML therapy and positive for an IDH2 mutation will be enrolled worldwide.

4.2. Inclusion Criteria

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

1. Subject is ≥ 60 years of age at the time of signing the ICF
2. Subject has primary (ie, de novo) or secondary (progression of MDS or myeloproliferative neoplasms ([MPN], or therapy-related) AML according to WHO classification (Appendix B)
3. Subject has received second- or third-line of AML therapy (see Appendix G for the definition of prior AML line; note that, for subjects having AML secondary to prior higher risk [Intermediate-2 or High risk according to the International Prognostic Scoring System] MDS treated with a hypomethylating agent [eg, azacitidine or decitabine], the hypomethylating therapy can be counted as a line if there is disease progression to AML during or shortly [eg, within 60 days] after the hypomethylating therapy.)
4. Subject has the following disease status:
    a. Refractory to or relapsed after second- or third-line of intensive therapy for AML (eg, the "7 + 3" regimen):

       at least 5% leukemic blasts in bone marrow (the minimum number of treatment cycles of the intensive therapy is per the investigator's discretion); or

    b. Refractory to or relapsed after second- or third-line low-intensity AML therapy (eg, LDAC, azacitidine or decitabine):

       at least 5% leukemic blasts in bone marrow after at least 2 treatment cycles
5. Subject is eligible for and willing to receive the pre-selected CCR treatment option, according to the investigator's assessment (Note: Subjects with degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionizing radiation, should not receive cytarabine.)
6. Subject has Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (Appendix D)
7. Subject has IDH2 gene mutations tested centrally (using the "investigational use only" PCR assay, Abbott RealTime IDH2) in samples of bone marrow aspirate **and** peripheral blood, and confirmed positive in bone marrow aspirate **and/or** peripheral blood. (Note: in the event that the central laboratory result is delayed and precludes acute clinical management of a subject who has confirmed IDH2 gene mutation by local evaluation, the subject may be eligible for randomization with approval by the Medical Monitor.)

8. Subject has adequate organ function defined as:
   - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) ≤ 3 x upper limit of normal (ULN), unless considered due to leukemic organ involvement, following review by the Medical Monitor; and
   - Serum total bilirubin ≤ 1.5 x ULN, unless considered due to Gilbert's syndrome (eg, a gene mutation in UGT1A1) or leukemic organ involvement, following review by the Medical Monitor; and
   - Creatinine clearance > 30 mL/min based on the Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR):

     GFR (mL/min/1.73 m2) = $175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$
9. Females of childbearing potential (FCBP)* may participate, providing they meet the following conditions:
   - Agree to practice true abstinence** from sexual intercourse or to use highly effective contraceptive methods (eg, combined [containing estrogen and progestogen] or progestogen-only associated with inhibition of ovulation, oral, injectable, intravaginal, patch, or implantable hormonal contraceptive; bilateral tubal occlusion; intra-uterine device; intrauterine hormone-releasing system; or male partner sterilization [note that vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the FCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success]) at screening and throughout the study, and for 4 months following the last study treatment (6 months following the last dose of cytarabine); and
   - Have a negative serum β-subunit of human chorionic gonadotropin (β-hCG) pregnancy test (sensitivity of at least 25 mIU/mL) at screening; and
   - Have a negative serum or urine (investigator's discretion under local regulations) β-hCG pregnancy test (sensitivity of at least 25 mIU/mL) within 72 hours prior to the start of study treatment in the Treatment Phase (note that the screening serum pregnancy test can be used as the test prior to the start of study treatment in the Treatment Phase if it is performed within the 72-hour timeframe).
10. Male subjects must agree to practice true abstinence** from sexual intercourse or to the use of highly effective contraceptive methods (as described above) with non-pregnant

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* A female of childbearing potential is a sexually mature woman who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months).

** True abstinence is only accepted as a method of contraception when it is the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not considered to be acceptable methods of contraception.

female partners of childbearing potential at screening and throughout the course of the study, and should avoid conception with their partners during the course of the study and for 4 months following the last study treatment (6 months following the last dose of cytarabine; 6 months following the last dose of azacitidine in Canada)

11. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
12. Subject is willing and able to adhere to the study visit schedule and other protocol requirements

4.3. Exclusion Criteria

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

1. Subject is suspected or proven to have acute promyelocytic leukemia based on morphology, immunophenotype, molecular assay, or karyotype (Appendix B)
2. Subject has AML secondary to chronic myelogenous leukemia (CML; Appendix C)
3. Subject has received a targeted agent against an IDH2 mutation
4. Subject has received systemic anticancer therapy or radiotherapy < 14 days prior to the start of study treatment. Note that hydroxyurea is allowed prior to the start of study treatment for the control of leukocytosis (however, hydroxyurea should not be given within 72 hours prior to and after administration of azacitidine).
5. Subject has received non-cytotoxic or investigational agents < 14 days or 5 half-lives, whichever is longer, prior to the start of study treatment
6. Subject has undergone HSCT within 60 days prior to the start of study treatment, or on immunosuppressive therapy post HSCT at the time of screening, or with clinically significant graft-versus-host disease (GVHD). The use of a stable dose of oral steroid post-HSCT and/or topical steroids for ongoing skin GVHD is permitted.
7. Subject has persistent, clinically significant non-hematologic toxicities from prior therapies
8. Subject has or is suspected of having central nervous system (CNS) leukemia. Evaluation of cerebrospinal fluid is only required if CNS involvement by leukemia is suspected during screening.
9. Subject has active uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment)
10. Subject has immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation
11. Subject has significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) class III or IV congestive heart failure (Appendix E); acute coronary syndrome (ACS); and/or stroke; or left

ventricular ejection fraction (LVEF) < 40% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan obtained within 28 days prior to the start of study treatment

12. Subject has prior history of malignancy, other than MDS, MPN or AML, unless the subject has been free of the disease for ≥ 1 year prior to the start of study treatment. However, subjects with the following history/concurrent conditions are allowed:
    - Basal or squamous cell carcinoma of the skin
    - Carcinoma in situ of the cervix
    - Carcinoma in situ of the breast
    - Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, node, metastasis clinical staging system)
13. Subject is known seropositive or active infection with human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)
14. Subject is known to have dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally
15. Subjects has uncontrolled hypertension (systolic blood pressure [BP] > 180 mmHg or diastolic BP > 100 mmHg)
16. Subject is a pregnant or lactating female
17. Subject has known or suspected to have hypersensitivity to any of the components of study treatment
18. Subject is taking those medications (listed in Section 8.2) that are known to prolong QT interval unless the subject can be transferred to other medications at least 5 half-lives prior to the start of study treatment
19. Subject has QTc interval (ie, Fridericia's correction [QTcF]) ≥ 450 ms or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome) at screening
20. Subject is taking the following sensitive CYP substrate medications that have a narrow therapeutic range are excluded from the study unless the subject can be transferred to other medications at least 5 half-lives prior to the start of study treatment: paclitaxel and docetaxel (CYP2C8), phenytoin (CYP2C9), S-mephenytoin (CYP2C19), thioridazine (CYP2D6), theophylline, and tizanidine (CYP1A2)
21. Subject is taking the breast cancer resistance protein (BCRP) transporter-sensitive substrate rosuvastatin should be excluded from the study unless the subject can be transferred to other medications at least 5 half-lives prior to the start of study treatment
22. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
23. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study

24. Subject has any condition that confounds the ability to interpret data from the study

5. TABLE OF EVENTS

Table 3: Table of Events

Events	Screening Phase	Treatment Phase [a]								Follow-up Phase [a]
	Screening	28-day cycles							EOT [b]	Follow-up
		Cycles 1 to 2				Cycles 3 to 4		Cycle 5 and beyond		
	Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		
Informed Consent	× [c]									
IVRS Registration and Calls	×	× [d]				×		×	×	
Inclusion & Exclusion Criteria	×	× [e, f]								
Demographics	×									
Initial AML Diagnosis	×									
Prior AML Therapies	×									
AML Disease Status	× [g]									
Central Testing of IDH2 Gene Mutations on BMA and PB	× [g]									
Medical History	×									
Prior Medications and Procedures	× [h]									
Eligibility of CCR Options	× [i]									
EORTC QLQ-C30 and EQ-ED-5L		×				×		×	×	
ECOG Performance Status	×	×				×		×	×	
Physical Exam [j]	×	×				×		×	×	
Vital Signs	×	×	×	×	×	×	×	×	×	

Table 3: Table of Events (Continued)

Events	Screening Phase	Treatment Phase [a]								Follow-up Phase [a]
	Screening	28-day cycles							EOT [b]	Follow-up
		Cycles 1 to 2				Cycles 3 to 4		Cycle 5 and beyond		
	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		
Height	×									
Body Weight	×	×				×		×	×	
BSA Calculation [k]	×	×				×		×		
ECHO [l]	× [m]	As clinically indicated								
12-Lead ECG [l]	×	×		×		×		×	×	
Pregnancy Test (FCBP only) [n]	× [o]	× [l, p]				× [l]		× [l]	× [l]	
Urinalysis [o]	×	As clinically indicated								
Coagulation Laboratory [o]	×									
Hematology Laboratory [o]	×	×	×	×	×	×	×	×	×	× [q]
Chemistry Laboratory [o]	×	×		×		×		×	×	
UGT1A1 Gene Mutation Test [o] (for Diagnosis of Gilbert's syndrome; refer to Section 4.2)	×									
Cardiac Markers [o]		× [f]	× [r]							
Fasting (preferred) Lipid Panel [o]		×				× [s]				
Adverse Event	Continuous starting after signing ICF until 28 days after the last study treatment or until the EOT visit, whichever is longer									
[redacted]										
Concomitant Medications and Procedures		Continuous until 28 days after the last study treatment or until the EOT visit, whichever is longer								
Transfusions	× [u]									

Table 3: Table of Events (Continued)

Events	Screening Phase	Treatment Phase [a]								Follow-up Phase [a]
		28-day cycles								
	Screening	Cycles 1 to 2				Cycles 3 to 4		Cycle 5 and beyond	EOT [b]	Follow-up
	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		
BMA for Assessing Disease Status /Response to Treatment [v]	× [g]	× [w]				× [x]		× [y]	× [z]	× [q]
[redacted]										
BMB [dd]	× [g]	× [w]				× [x]		× [y]	× [z]	× [q]
PB Smear	× [g]	× [w]				× [x]		× [y]	× [z]	× [q]
Cytogenetics Testing	× [g]	× [w, ee]				× [x, ee]		× [y, ee]	× [z, ee]	× [q, ee]
Response and HI		× [w]				× [x]		× [y]	× [z]	× [q]
[redacted]										

Table 3: Table of Events (Continued)

Events	Screening Phase	Treatment Phase [a]								Follow-up Phase [a]
		28-day cycles								
	Screening	Cycles 1 to 2				Cycles 3 to 4		Cycle 5 and beyond	EOT [b]	Follow-up
	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		
Treatment Accountability [jj]		× [kk]				×		×	×	
IP Dispensation		×				×		×		
Treatment Administration		See Section 7.2 for details								
Survival Follow-up										× [ll]
Subsequent AML Therapies/ Response / Disease Status to Subsequent AML Therapies per Investigator										× [ll]

Abbreviations: AML = acute myeloid leukemia; β- hCG = β-subunit of human chorionic gonadotropin; BMA = bone marrow aspirate; BMB = bone marrow biopsy; BSA = body surface area; CCR = conventional care regimen; CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; ECHO = echocardiogram; eCRF = electronic case report form; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC= European Organization for Research and Treatment of Cancer; FCBP = female of childbearing potential; EOT = End of Treatment; HI = hematologic improvement; HRQoL = Health-related Quality of Life; HSCT = hematopoietic stem cell transplantation; ICF = informed consent form; IDH2 = isocitrate dehydrogenase isoform 2; IP = investigational product; IVRS = Interactive Voice Response System; IWG = International Working Group; [redacted] PB = peripheral blood; PD = progressive disease; SOC = standard of care; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1 family, polypeptide A1.

[a] Study Treatment is to be initiated on Day 1 of each treatment cycle. One treatment cycle (one month) is considered as 28 days (ie, 4 weeks). Unless noted otherwise, an administrative window of ± 3 days is permitted for all subsequent visits after the start of study treatment in the Treatment Phase. Day 1 of Cycles 2 and beyond may be delayed from Day 28 of the prior cycle in order for subjects to recover from toxicity and meet criteria for initiating each treatment cycle (Section 7.2). The study visit window for EOT or monthly-scheduled survival follow-up is ± 7 days.

[b] See Section 6.2.3 for details.

[c] Including informed consent for mandatory genetic testing [redacted].

[d] The subject should start study treatment (ie, Day 1 of Cycle 1) within 3 days after randomization.

[e] Subject should continue to be eligible for study entry prior to the start of study treatment on Day 1 of Cycle 1.

[f] Cycle 1 only.
[g] See Section 6.1 for details regarding collecting BMA, BMB, PBS and cytogenetics at screening for assessing AML disease status, collecting BMA and PB at screening for central testing IDH gene mutations [redacted]. In the event that the central laboratory result is delayed and precludes acute clinical management of a subject who has confirmed IDH2 gene mutation by local evaluation, the subject may be eligible for randomization with approval by the Medical Monitor.
[h] All prior medications (prescription and non-prescription) taken and treatment procedures received from the 4-week period (ie, 28 days) prior to starting study treatment (including those prior to the start of study treatment on Day 1 of Cycle 1), and all prior anticancer therapies, regardless of discontinuation date of treatment.
[i] Documentation of CCR treatment option selected by the investigator must occur prior to randomization.
[j] Source documented only.
[k] The BSA calculation is per the Dubois & Dubois formula: BSA (m^2) = weight $(kg)^{0.425}$ x height $(cm)^{0.725}/139.2$. Where applicable, the dose should be calculated on Day 1 of each treatment cycle.
[l] These assessments will be done locally.
[m] The screening ECHO does not need to be repeated if a prior ECHO or multi-gated acquisition (MUGA) scan has been performed within 28 days prior to the start of study treatment.
[n] Pregnancy test is required for all FCBPs (see Section 4.2 for the definition). Serum β-hCG pregnancy test (sensitivity of at least 25 mIU/mL) will be performed centrally at screening. For FCBP subjects, a local serum or urine (investigator's discretion under local regulations) β- hCG pregnancy test (sensitivity of at least 25 mIU/mL) is to be done within 72 hours prior to study treatment administration on Day 1 of every treatment cycle in the Treatment Phase and at the EOT visit. Negative results are required for study treatment administration.
[o] These assessments will be done centrally. Fasting is recommended, particularly for subjects who experience clinically meaningful elevations of lipids, per the investigator's assessment.
[p] A local serum or urine (investigator's discretion under local regulations) pregnancy test (sensitivity of at least 25 mIU/mL) is to be done within 72 hours prior to the start of study treatment in the Treatment Phase for FCBP only (note that the screening central serum pregnancy test can be used as the test prior to the start of study treatment in the Treatment Phase if it is performed within the 72-hour timeframe).
[q] Whenever response/disease status is assessed in the Follow-up Phase (ie, every 12 weeks [± 28 days]). See Section 6.3 for details.
[r] Day 1 (± 14 days) of every 3rd cycle (eg, Cycles 3, 6, 9, etc) or more frequently per standard institutional practice. Not necessary for the EOT visit if last performed within 14 days.
[s] Day 1 of Cycle 3 and Day 1 (± 28 days) of every 6th cycle (eg, Cycles 6, 12, 18, etc) or more frequently per standard institutional practice. Not necessary for the EOT visit if last performed within 28 days.
[redacted]
[u] Including type, number of units, reasons and date of transfusions taken ≤ 8 weeks prior to the start of study treatment through 28 days after the last study treatment or until the EOT visit, whichever is longer. Thereafter, transfusions will continue to be collected until the initation of the first subsequent AML therapy after discontinuation from study treatment, death, lost to follow-up, withdrawal of consent for further data collection, or the End of Trial, whichever occurs first.
[v] In addition to the frequency specified in the table, samples will also be collected if clinically indicated (eg, confirmation of CR/CRi/CRp, morphologic relapse after CR/CRi/CRp or PD by a repeated bone marrow assessment at least 1 month later) or required for toxicity assessment.
[w] Within 7 days prior to study treatment administration on Day 1 of Cycle 2.
[x] Within 7 days prior to study treatment administration on Day 1 of Cycle 3.

[y] Within 7 days prior to study treatment administration on Day 1 of Cycle 5 and Day 1 of every 2nd cycle thereafter (eg, Cycles 7, 9, etc).
[z] Not necessary for the EOT visit if last performed within 28 days.

[redacted]

[dd] A bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice. A bone marrow biopsy must be collected if adequate aspirate is not attainable.
[ee] If the bone marrow aspirate is obtained for confirming CR/CRi/CRp, morphologic relapse after CR/CRi/CRp or PD, a sample of the bone marrow aspirate is to be sent to the local or central cytogenetics laboratory (for sites without local analysis capability) for standard metaphase preparation and analysis of a minimum of 20 metaphase cells. A bone marrow biopsy can be used for cytogenetics testing if adequate aspirate is not attainable (note that specific handling of the biopsy is required for cytogenetics testing).

[redacted]

[jj] Including diary cards, if utilized. See Section 7.6 for details.
[kk] Cycle 2 only.
[ll] Every 4 weeks (± 7 days) for survival follow-up until death, lost to follow-up, withdrawal of consent for further data collection or the End of Trial, whichever occurs first. Subsequent AML therapies and investigator-assessed response/disease status to subsequent AML therapies should be collected at the same time schedule. See Section 6.3 for details.

6. PROCEDURES

Any questions regarding the protocol should be directed to the Medical Monitor or designee.

Written ICFs must be obtained before any study evaluations are performed and any samples are collected per local regulations during the course of the study.

6.1. Screening Phase

Screening evaluations start from ICF signing and must be completed within 28 days prior to the start of study treatment, unless noted otherwise below. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

The following will be performed at screening as specified in the Table of Events, Table 3, after written ICFs have been obtained:

- Registration of screening in IVRS
- Inclusion and exclusion criteria
- Demographics (age, sex, race, and ethnicity)
- Information supporting the initial diagnosis of AML by local pathology and cytogenetics review, including reports of bone marrow aspirate and/or biopsy, peripheral blood smear, cytogenetics and other tests if pertinent
- Prior AML therapies including surgery, radiation, systemic or any other therapy for the subject's AML disease, particularly induction/re-induction/salvage chemotherapies, consolidation or maintenance therapies, HSCT, low-intensity AML therapies such as azacitidine, decitabine or LDAC, or other medications considered supportive care for AML, regardless of discontinuation date of treatment
- Information supporting CR/CRi/CRp attained during prior AML therapies by local pathology and cytogenetics review, including reports of bone marrow aspirate and/or biopsy, peripheral blood smear, cytogenetics, and other pertinent tests
- AML disease status at screening determined by local pathology and cytogenetics review and confirmed retrospectively by central review. Therefore, bone marrow aspirate (or biopsy if adequate aspirate is not attainable) must be collected at screening so slides of bone marrow aspirate (and/or biopsy) and peripheral blood smear are available for both the local and the central pathology reviewers. A bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice. Whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared. In addition, a sample of the screening bone marrow aspirate is to be sent to the local or central cytogenetics laboratory (for sites without local analysis capability) for standard metaphase preparation and analysis of a minimum of 20 metaphase cells. A bone marrow biopsy can be used for cytogenetics testing if adequate aspirate is not attainable (note that specific handling of the biopsy is required for cytogenetics testing).

The retrospective central review of screening bone marrow aspirates and/or biopsies, peripheral blood smears and cytogenetics will be conducted by personnel blinded to study treatment. The central assessments will be used to confirm AML disease status at screening. If central review and local review disagree on AML disease status of a subject at screening, a third party reviewer will adjudicate and make the final assessment. If the subject was centrally confirmed to be ineligible for the study, the subject will be allowed to remain in the study, but will be excluded from the modified intent-to-treat (mITT) population (Section 9.2.2).

Instructions for submission slides of bone marrow aspirate (and/or biopsy) and peripheral blood smear, and pertinent reports for central review are provided in the Study Reference and/or Study Central Laboratory Manual.

- Subject has IDH2 gene mutations tested centrally in samples of bone marrow aspirate **and** peripheral blood, and confirmed positive in bone marrow aspirate **and/or** peripheral blood. (Note: in the event that the central laboratory result is delayed and precludes acute clinical management of a subject who has confirmed IDH2 gene mutation by local evaluation, the subject may be eligible for randomization with approval by the Medical Monitor.)

  The detection and identification of IDH2 mutations (if present) will be assessed by Abbott RealTime IDH2 using a partially automated system entailing extraction and amplification of deoxyribonucleic acid (DNA) with specific primers and probes. The device (test) has been developed by Abbott Molecular Inc. and is used to detect and identify IDH2 mutations in subjects' bone marrow aspirate and peripheral blood specimens. The commercial test, which has been approved by FDA, is equivalent to the investigational test in the study.

  Refer to the Study Reference and/or Study Laboratory Manual for sample collection, processing, storage, and shipment procedures.

- Medical history including all relevant current medical conditions and medical conditions diagnosed/ occurring prior to screening
- Prior medications including those taken ≤ 28 days prior to the start of study treatment and all prior anticancer therapies, regardless of discontinuation date of treatment
- Prior procedures including those occurring ≤ 28 days prior to the start of study treatment and all prior anti-cancer procedures, regardless of discontinuation date of treatment
- Documentation of the CCR treatment option selected by the investigator prior to randomization
- ECOG performance status
- Physical examination: information about the screening physical examination must be present in the subject's source documentation. Significant findings must be included on the appropriate eCRF page.
- Vital signs including temperature, blood pressure, pulse rate and respiratory rate

- Height (only collected once at screening)
- Body weight
- Body surface area (BSA) calculation per the Dubois & Dubois formula:
  BSA (m^2) = weight (kg)$^{0.425}$ x height (cm)$^{0.725}$/139.2
- The following laboratory assessments will be done locally:
  - ECHO (not required if a prior ECHO or MUGA scan has been performed within 28 days prior to the start of study treatment)
  - 12-lead ECG will be assessed by a physician trained in ECG interpretation as normal, abnormal - not clinically significant, or abnormal - clinically significant. Intervals including PR, QRS, QT and RR will be collected, as well as heart rate and rhythm. Abnormal finding(s) will be reported on the appropriate eCRF page. For a given subject, ECG interpretations should be conducted by the same physician throughout the study as much as possible, with a consistent approach for the QT interval analysis (eg, pre-cordial leads and lead II).
- The following laboratory assessments will be done centrally:
  - Serum β-hCG pregnancy test (sensitivity of at least 25 mIU/mL) is required for all FCBPs (see Section 4.2 for the definition)
  - Urinalysis including examination by a standard dipstick test for specific gravity, glucose, ketones, blood, pH, and protein, and microscopic analysis if indicated
  - Coagulation test including prothrombin time (PT) with international normalized ratio (INR) and partial thromboplastin time (PTT)
  - Hematology panel including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC) count (with differential), absolute neutrophil count (ANC) and platelet count
  - Chemistry panel including sodium, potassium, calcium, magnesium, chloride, phosphorus, CO_2, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase (ALP), bilirubin (total and direct), uric acid, lactate dehydrogenase (LDH), AST/SGOT, ALT/SGPT, gamma glutamyl transpeptidase (GGT), amylase and lipase
  - UGT1A1 gene mutation test performed on peripheral blood samples for diagnosis of Gilbert's syndrome (refer to the inclusion criterion regarding serum total bilirubin in Section 4.2)
- Assessing AEs [redacted] start when the subject signs the ICF
- Transfusion history including the type, number of units, reason, and date of transfusions for the 8 weeks prior to the start of study treatment

Information to be Collected on Screening Failures

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

Randomization

Eligible subjects will be randomized in a central IVRS in a 1:1 ratio to receive either the AG-221 treatment or the CCR treatment option pre-selected by the investigator. Randomization will be stratified by prior intensive therapy for AML (yes versus no), primary refractory (yes versus no), and prior allogeneic HSCT for AML (yes versus no).

The study treatment should be initiated within 3 days after randomization.

6.2. Treatment Phase

The subject should continue to be eligible for study entry prior to the start of study treatment on Day 1 of Cycle 1. Study Treatment is to be initiated on Day 1 of each treatment cycle. One treatment cycle (one month) is considered as 28 days (ie, 4 weeks). Unless noted otherwise, an administrative window of ± 3 days is permitted for all subsequent visits after the start of study treatment in the Treatment Phase. Day 1 of Cycles 2 and beyond may be delayed from Day 28 of the prior cycle in order for subjects to recover from toxicity and meet criteria for initiating each treatment cycle (see Section 7.2 for details).

The following evaluations will be performed during study treatment at the frequency specified in the Table of Events, Table 3, or more frequently if clinically indicated. The evaluations should be performed prior to dosing on scheduled clinical visit day, unless otherwise specified. For each evaluation, the same parameters as required at screening or on Day 1 of Cycle 1 should be evaluated.

- Registration of the start of each treatment cycle in IVRS (where applicable)

- HRQoL (EORTC QLQ-C30 and EQ-ED-5L questionnaires; Section 6.9)
- Treatment accountability (where applicable; also refer to Section 7.5)
- ECOG performance status
- Physical examination, vital signs and body weight. Significant findings are to be reported on the appropriate eCRF page.
- Body surface area calculation. Where applicable, the dose should be calculated on Day 1 of each treatment cycle.
- The following laboratory assessments will be done locally:
  - ECHO if clinically indicated
  - 12-lead ECG. Abnormal finding(s) will be reported on the appropriate eCRF page.
  - A serum or urine (investigator's discretion under local regulations) β-hCG pregnancy test (sensitivity of at least 25 mIU/mL) is to be done within 72 hours prior to study treatment administration on Day 1 of each treatment cycle (for FCBPs only; note that the central serum pregnancy test at screening can be used as the test prior to the start of study treatment in the Treatment Phase if it is performed within the 72-hour timeframe). The subject may not receive study treatment until the investigator has verified that the result of the pregnancy test is negative.
- The following laboratory assessments will be done centrally:
  - Urinalysis and/or coagulation test if clinically indicated
  - Hematology panel
  - Chemistry panel
  - Cardiac marker troponin I
  - Fasting (preferred) lipid panel including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides. Fasting is recommended, particularly for subjects who experience clinically meaningful elevations of lipids, per the investigator's assessment.
- Continuous evaluations of AEs, [redacted] concomitant medications and procedures, and transfusions
- Bone marrow aspirate (or biopsy if adequate aspirate is not attainable) samples will be collected for assessing response during study treatment. As specified in the Table of Events, Table 3, the frequency is within 7 days prior to study treatment administration on Cycles 2 and 3, every 2nd cycle thereafter (eg, Cycles 5, 7, 9, etc), and if clinically indicated (eg, confirmation of CR/CRi/CRp, morphologic relapse after CR/CRi/CRp or PD by a repeated bone marrow assessment at least 1 month later) or required for toxicity assessment. A bone marrow biopsy can be collected in

conjunction with an aspirate if it is standard institutional practice or if clinical indicated (eg, evaluation of bone marrow cellularity). Whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared. In addition, whenever a bone marrow aspirate is obtained for confirming CR/CRi/CRp, morphologic relapse after CR/CRi/CRp or PD, a sample of the bone marrow aspirate is to be sent to the local or central cytogenetics laboratory (for sites without local analysis capability) for standard metaphase preparation and analysis of a minimum of 20 metaphase cells. A bone marrow biopsy can be used for cytogenetics testing if adequate aspirate is not attainable (note that specific handling of the biopsy is required for cytogenetics testing). Bone marrow aspirate and/or biopsy, peripheral blood smear and cytogenetics collected after the start of study treatment for response assessment must be available for both local and central review. Instructions for submission slides of bone marrow aspirate (and/or biopsy) and peripheral blood smear, and pertinent reports for central review are provided in the Study Reference and Study Central Laboratory Manuals

- Response to treatment and HI will be assessed whenever bone marrow samples are collected for response assessment (see above)

- Treatment dispensing and administration (where applicable; refer to Section 7)

6.2.1. Baseline

Unless noted otherwise for a particular assessment, results obtained just prior to the start of study treatment on Day 1 of Cycle 1 will serve as the baseline values. If not available, the most recent screening results prior to the start of study treatment on Day 1 of Cycle 1 will be considered the baseline values. Transfusions history includes the type, number of units, reason, and date of transfusions for the 8 weeks prior to the start of study treatment on Day 1 of Cycle 1. EORTC QLQ-30 and EQ-5D are to be completed prior to the start of study treatment on Day 1 of Cycle 1 and prior to interaction with study personnel.

6.2.2. Unscheduled Visits

Should it become necessary to repeat an evaluation (eg, laboratory tests or ECG), the results of the repeat evaluations should be entered as appropriate in additional unscheduled visit pages of the eCRF.

6.2.3. End of Treatment

An EOT evaluation will be performed for subjects who are withdrawn from study treatment for any reason as soon as possible after the decision to permanently discontinue study treatment has been made. An administrative window of ± 7 days is permitted for the EOT visit, unless noted otherwise. If a subject is discontinued during a regularly-scheduled visit, all EOT evaluations should be completed at that visit.

The following evaluations will be performed as specified in the Table of Events, Table 3. For each evaluation, the same parameters as required at screening or on Day 1 of Cycle 1 should be evaluated.

- Registration of treatment discontinuation in IVRS
- HRQoL (EORTC QLQ-C30 and EQ-ED-5L questionnaires)
- Treatment accountability (where applicable; refer to Section 7.5)
- ECOG performance status
- Physical examination, vital signs and body weight. Significant findings are to be reported on the appropriate eCRF page.
- The following laboratory assessments will be done locally:
  - ECHO if clinically indicated
  - 12-lead ECG
  - A serum or urine (investigator's discretion under local regulations) β-hCG pregnancy test (sensitivity of at least 25 mIU/mL) (for FBCPs only)
- The following laboratory assessments will be done centrally:
  - Urinalysis and/or coagulation test if clinically indicated
  - Hematology panel
  - Chemistry panel

- Cardiac marker (not necessary for the EOT visit if it was last performed within 14 days unless clinically indicated)
- Fasting (preferred) lipid panel (not necessary for the EOT visit if it was last performed within 28 days unless clinically indicated)

- Evaluations of AEs, [redacted] concomitant medications, concomitant procedures and transfusions (monitored through 28 days after the last study treatment or until the EOT visit, whichever is longer)
- Bone marrow aspirate and/or biopsy, peripheral blood smear and, if applicable, cytogenetics, for response assessment (not necessary for the EOT visit if it was last performed within 28 days unless clinically indicated)
- Response to treatment and HI will be assessed if bone marrow samples are collected for assessing response at the EOT visit (see above)

[redacted]

6.3. Follow-up Phase

All subjects discontinued from study treatment for any reason other than withdrawal of consent for follow-up will continue to have the following assessments in the Follow-up Phase:

- AEs, [redacted] concomitant medications, concomitant procedures and transfusions for 28 days after the last study treatment or the EOT visit, whichever is longer.

  Thereafter, SAEs made known to the investigator at any time that are suspected of being related to study treatment, as described in Section 10.1.
- Transfusions [redacted] will continue to be collected until the initation of the first subsequent AML therapy after discontinuation from study treatment, death, lost to follow-up, withdrawal of consent for further data collection, or the End of Trial, whichever occurs first.
- Bone marrow aspirate and/or biopsy, peripheral blood smear and, if applicable, cytogenetics, available for both local and central review for assessing response or

disease status, every 12 weeks (± 28 days) or more frequent if clinically indicated until PD, the initation of the first subsequent AML therapy after discontinuation of study treatment, death, lost to follow-up, withdrawal of consent for further data collection, or the End of Trial, whichever occurs first.

- Response/disease status and HI will be assessed whenever bone marrow samples are collected for assessing response or disease status (see above)

- Survival follow-up every 4 weeks (± 7 days) until death, lost to follow-up, withdrawal of consent for further data collection, or the End of Trial, whichever occurs first. Subsequent AML therapies should be collected at the same schedule as survival follow-up.
- Investigator-assessed response/ disease status to subsequent AML therapies will be collected. Specifically, the best response to a subsequent AML therapy and the first date achieving the best response, and progressive disease/relapse date during or after a respective subsequent AML therapy should be reported.
- Survival follow-up, subsequent AML therapies, and response/ disease status to subsequent AML therapies may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.
- Females of childbearing potential should avoid becoming pregnant for 4 months after the last study treatment (6 months after the last dose of cytarabine), and male subjects and their partners should avoid conception for 4 months after the last study treatment (6 months after the last dose of cytarabine; 6 months after the last dose of azacitidine in Canada).

6.4. Safety Assessment

Safety assessments include physical examination, vital signs, ECG, hematology, serum chemistry, cardiac markers, fasting (preferred) lipid panel, pregnancy testing (for FCBP subjects only), AEs, concomitant medications and procedures, and transfusions, will be performed at the frequency specified in Table 3 or more frequently if clinically indicated. After screening, ECHO, urinalysis and coagulation will be performed if clinically indicated.

6.4.1. Adverse Events

Refer to Section 10 for AE reporting. Information about common side effects already known about AG-221 and azacitidine can be found in the respective IBs or will be communicated between IB updates in the form of Investigator Notifications. Refer to United Kingdom (UK) Summary of Product Characteristics (SmPC) for information about common side effects already known about cytarabine. This information about common side effects will also be included in the subject ICF and should be discussed with the subject as needed during the study.

6.4.2. Urinalysis, Coagulation, Hematology, Serum Chemistry, Cardiac Markers and Fasting (Preferred) Lipid Panel

All samples should be sent to the central laboratory. In the event that an immediate laboratory assessment is required to acutely manage a subject (eg, monitoring ALT increases of ≥ 3 x ULN; Appendix P), local laboratory tests may be used. In addition to collecting the local laboratory sample, a second sample should be collected and sent to the central laboratory.

Refer to Section 10.3 for information regarding abnormal laboratory values or whether test results constitute an AE.

6.5. Efficacy Assessment

6.5.1. Disease Status or Response to Study Treatment

Bone marrow aspirate (or biopsy if adequate aspirate is not attainable) samples will be collected for assessing disease status or response to study treatment at the frequency specified in Table 3 or more frequently if clinically indicated.

A bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice or if clinical indicated (eg, evaluation of bone marrow cellularity). Whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared.

In addition, whenever a bone marrow aspirate is obtained for confirming CR/CRi/CRp, morphologic relapse after CR/CRi/CRp or PD, a sample of the bone marrow aspirate is to be sent to the local or central cytogenetics laboratory (for sites without local analysis capability) for standard metaphase preparation and analysis of a minimum of 20 metaphase cells. A bone marrow biopsy can be used for cytogenetics testing if adequate aspirate is not attainable (note that specific handling of the biopsy is required for cytogenetics testing).

Bone marrow aspirate and/or biopsy, peripheral blood smear and cytogenetics collected throughout study must be available for both local and central review. A retrospective central review of all bone marrow aspirates and/or biopsies, peripheral blood smears and cytogenetics collected throughout study will be conducted by personnel blinded to subject treatment. The central cytogenetic review will provide standardized analysis and reporting for all subjects, regardless of the laboratory performing the initial analysis (local or central). The central assessments will be used in the statistical analyses. Disagreement between central and local assessments will be adjudicated by a third party reviewer and the adjudicated assessment will be used in the statistical analyses.

Response to study treatment will be assessed by the investigators and retrospectively by a blinded IRAC according to modified IWG AML response criteria (Appendix F) through

collection of central hematology parameters, central assessments of bone marrow aspirates and/or biopsies, peripheral blood smears and cytogenetics, and results of other pertinent tests.

Instructions for submission slides of bone marrow aspirate (and/or biopsy) and peripheral blood smear, and pertinent reports for central review are provided in the Study Reference and Study Central Laboratory Manuals.

In addition, investigator-assessed response/ disease status to subsequent AML therapies will be collected (see the details in Section 6.3).

6.5.2. Hematologic Improvement

Hematologic improvement will be assessed by the investigators and retrospectively by a blinded IRAC according to IWG MDS HI criteria (Appendix H) through collection of transfusion records and central hematology parameters.

6.5.3. Survival

Refer to Section 6.3 for survival follow-up.

[redacted]

6.9. Quality-of-Life

Two instruments, the European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC QLQ-C30) and EuroQoL Group EQ-5D, will be used for HRQoL.

The EORTC QLQ-30 (Aaronson, 1993) is a validated quality of life measure applicable to subjects with any cancer diagnosis. It is composed of 30 items that address general physical symptoms, physical functioning, fatigue and malaise, and social and emotional functioning. Subscale scores are transformed to a 0 to 100 scale, with higher scores on functional scales indicating better function and higher scores on symptom scales indicating worse symptoms. The EORTC QLQ-C30 is available in many languages. This instrument takes 10 to 15 minutes to administer. The EORTC QLQ-C30 data will be captured using a portable electronic tablet computer. See Appendix I for an example.

The EQ-5D is a standardized instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status, and is applicable to a wide range of health conditions and treatments. The EQ-5D is available in many languages and it takes approximately 5 minutes to complete. EQ-5D data will be captured using a portable electronic tablet computer. See Appendix J for an example.

It is important that every subject completes all assessments of EORTC QLQ-30 and EQ-5D at every specified time point, prior to dosing and prior to interaction with study personnel, to minimize the amount of missing data.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

7.1.1. AG-221

AG-221 will be supplied by Celgene and labeled appropriately as investigational product (IP) for this study.

Celgene Corporation will supply AG-221 50-, 100-, 150- and 200-mg free-base equivalent strength tablets for oral administration. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products.

All tablets will be packaged in high density polyethylene (HDPE) bottles with a desiccant (silica gel) canister and child resistant closures with heat induction seal. All tablets should be swallowed whole, and should not be broken or chewed.

Bottles of AG-221 tablets must be stored according to the package label. The storage area should be secure and have limited access. AG-221 tablets will be monitored by the Sponsor for stability for the duration of the study.

7.1.2. Azacitidine

Azacitidine will be supplied by Celgene Corporation as a sterile lyophilized powder containing 100 mg of azacitidine and 100 mg of mannitol per vial.

Detailed instructions for preparation of SC azacitidine are provided in Appendix K.

7.1.3. Low-dose Cytarabine

Subjects randomized to LDAC treatment and located in countries where LDAC is designated as non-investigational product (NIP) may have cytarabine sourced locally by the clinical site. Subjects randomized to LDAC treatment and located in countries where LDAC is designated as IP will have cytarabine supplied and packaged by Celgene Corporation.

Please refer to the UK SmPC for more details on available formulations, preparation of SC cytarabine, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of cytarabine.

7.1.4. Intermediate-dose Cytarabine

Subjects randomized to IDAC treatment and located in countries where IDAC is designated as NIP may have cytarabine sourced locally by the clinical site. Subjects randomized to IDAC treatment and located in countries where IDAC is designated as IP will have cytarabine supplied and packaged by Celgene Corporation.

Please refer to the UK SmPC for more details on available formulations, preparation of IV cytarabine, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of cytarabine.

7.1.5. Best Supportive Care Only

Refer to Section 8 for details regarding BSC. Please refer to local prescribing information and local therapeutic guidelines for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of BSC (see the current version of prescribing information).

7.2. Treatment Administration and Schedule

Study treatment is to be initiated on Day 1 of each treatment cycle. The subject may not receive study treatment for each treatment cycle until all Day 1 procedures have been completed and all doses of study treatment from the prior treatment cycle are accounted for (where applicable). For FCBP subjects, a serum or urine (investigator's discretion under local regulations) β-hCG pregnancy test (sensitivity of at least 25 mIU/mL) must be performed within 72 hours prior to study treatment administration on Day 1 of each treatment cycle and verified negative.

No crossover between any of the treatment options, including the CCR treatment options, will be permitted during the course of study treatment. Any AML therapy other than the study-prescribed treatment is prohibited during the course of study treatment.

Subjects will be monitored for hematologic toxicity and non-hematologic toxicity with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) used as a guide for the grading of severity. Dosing interruptions or delays, or dose modifications may occur for managing toxicities and/or augmenting treatment response during study treatment.

Overdose, as defined for this protocol, refers to AG-221, azacitidine and cytarabine dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of AG-221, azacitidine and cytarabine assigned to a given subject, regardless of any associated adverse events or sequelae.

PO: any amount over the protocol-specified dose

IV: 10% over the protocol-specified dose

SC: 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. See Section 10 for the reporting of AEs associated with overdose.

Subjects can continue to receive study treatment provided that they benefit from study treatment and all protocol-specified criteria for continuing study treatment are met. Study treatment will be discontinued if the investigator has alternative therapies (eg, HSCT) and/or considers study treatment to be no longer beneficial to the subject, or the rapidity of change of disease state renders it unacceptable for further study treatment in the judgment of the investigator.

Refer to Section 11.1 for events that are considered sufficient reasons for discontinuing a subject from study treatment.

7.2.1. AG-221 Treatment

Subjects randomized to the AG-221 treatment arm will receive continuous 28-day cycles of AG-221 100 mg PO QD for 28 days. In addition, subjects may receive BSC per standard institutional practice and as deemed necessary by the investigator. In order to optimally benefit from the AG-221 treatment, the investigator should aim to treat subjects for at least 6 cycles or as long as subjects continue to benefit from the treatment until the End of Trial. Subjects may be discontinued from the treatment for any of the reasons detailed in Section 11.1.

7.2.1.1. Dispensation and Administration of AG-221

AG-221 will be dispensed on Day 1 of each treatment cycle and a quantity of AG-221 only sufficient for one treatment cycle will be dispensed. Subjects should be instructed to open the AG-221 packaging as close as possible to when they are going to take AG-221, inspect each AG-221 tablet and only take tablets that are totally intact (subjects should be instructed to return any tablet not totally intact to the clinic).

Subjects should be instructed to take their daily dose at approximately the same time each day. Each dose should be taken with a glass of water and consumed over as short a time as possible. Subjects should be instructed to swallow tablets whole and to not chew the tablets.

All efforts should be made to administer AG-221 on all of the scheduled days of each 28-day treatment cycle. A dose missed earlier in a day can be made up later that day as long as it is taken within 6 hours after the missed dose. If more than 6 hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose. Any missed doses should not be taken beyond the last scheduled day of AG-221 administration, but should be returned by the subject for AG-221 accountability.

If vomiting occurs shortly after a dose of AG-221 is administrated, that dose should not be made up later the same day. The subject should continue with the dosing schedule on the next day and inform the investigator about the vomiting event at the next visit.

7.2.1.2. Dose Modifications for AG-221

The investigator should contact the Medical Monitor for guidance on AG-221 dose modification, if needed.

Dose modification due to toxicities

If a certain level of toxicity (eg, Section 7.2.1.3) is observed after initiation of AG-221 treatment and considered as possibly or probably related to AG-221 treatment, AG-221 dosing can be interrupted or delayed. Upon resolution of the toxicity, dosing may be resumed with a one-level dose reduction from 100 mg QD to 50 mg QD. Any subject who is unable to tolerate 50 mg QD of AG-221 should be discontinued from study treatment.

If treatment is modified during the course of the study and benefit is demonstrated with a reduced level of dose, then that dose level should be maintained during the subsequent treatment cycles that are given unless toxicity develops. However, once reduced, if there is a need for augmenting treatment response as defined below, the AG-221 dose may be subsequently re-escalated back to the starting dose (ie, 100 mg QD), provided that the starting dose is tolerable.

Dose escalation for augmenting treatment responses

The AG-221 dose for the subsequent treatment cycles that are given may be increased from 100 mg QD to 200 mg QD if the following occurs:

- ANC < 0.5 x 10^9/L after being on AG-221 for the first cycle without ≥ Grade 3 AEs suspected by the investigator to be related to AG-221; or
- no partial remission (PR) achieved after being on AG-221 for at least 2 cycles without ≥ Grade 3 AEs suspected by the investigator to be related to AG-221; or
- evidence of morphologic relapse or PD

If benefit is demonstrated with an increased level of dose, then that dose level should be maintained during the subsequent treatment cycles that are given. However, once increased, the AG-221 dose may be reduced if a certain level of toxicity (eg, Section 7.2.1.3) is observed and considered as possibly or probably related to AG-221 treatment. A maximum of 3 steps of AG-221 dose reduction, stepwise first from 200 mg QD to 150 mg QD, second from 150 mg QD to 100 mg QD, and then last from 100 mg QD to 50 mg QD, are permitted in the event of toxicities, depending on the dose that the subject is on. Once reduced, the AG-221 dose should not be re-escalated unless there is evidence of morphologic relapse or PD. Any subject who is unable to tolerate 50 mg QD of AG-221 should be discontinued from study treatment.

7.2.1.3. Reference Toxicities During AG-221 Treatment

Hematologic toxicities

Hematologic toxicities include clinically significant hematologic toxicities of cytopenia (> 50% decrease from baseline [defined in Section 6.2.1]) and/or marrow cellularity < 5% on Day 28 or later from the start of AG-221 treatment in a treatment cycle without evidence of leukemia.

Non-hematologic toxicities

Non-hematologic toxicities include all clinically significant non-hematologic toxicities of ≥ Grade 3 with the exception of ≥ Grade 3 blood bilirubin increases in subjects with a UGT1A1 mutation. In subjects with a UGT1A1 mutation, blood bilirubin increases of > 5 × ULN may be considered clinically significant.

QT Prolongation

Subjects who experience prolongation of the heart rate-corrected QT interval, Fridericia's correction (QTcF) to > 480 msec (Grade ≥ 2) while treated with AG-221, should be promptly evaluated for causality of the QTc prolongation and managed according to the following guidelines:

- Levels of electrolytes (potassium, calcium and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medication with known QT prolonging effects.
- If no other cause is identified and the investigator believes it is appropriate, particularly if QTc remains elevated (after above measures have been implemented, or as determined by the investigator), AG-221 treatment may be interrupted, and an

ECG should be rechecked in approximately 1 week after the QTc prolongation was first observed or more frequently as clinically indicated.

- If QTc has recovered or improved and the investigator believes it is safe to do so, a re-challenge with AG-221 should be considered if held. ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTc reduction ≤ 480 msec.
- If Grade 2 (QTcF > 480 and ≤ 500 msec), the dose of AG-221 may be reduced without interruption of dosing. The AG-221 dose may be re-escalated to the prior dose in ≥ 14 days after QT prolongation has decreased to ≤ Grade 1.
    - If this is the second occurrence of QT prolongation, administration of AG-221 should continue at a reduced dose (ie, the dose may not be re-escalated).
- If Grade 3 (QTcF > 500 msec), hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. Dosing with AG-221 will be interrupted. If QTc returns to within 30 msec of baseline or < 450 msec within 14 days, treatment may be resumed at a reduced dose. The AG-221 dose cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.
- If Grade 4 (QTcF > 500 msec or > 60 msec change from baseline with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), subjects should be admitted to the hospital for continuous cardiac monitoring and discharged only after review by a cardiologist. Dosing with AG-221 should be permanently discontinued.

IDH Differentiation Syndrome

Subjects treated with AG-221 (enasidenib) have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

If differentiation syndrome is suspected, initiate oral or intravenous corticosteroids (eg, dexamethasone 10 mg every 12 hours) and hemodynamic monitoring until improvement. Taper corticosteroids only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe pulmonary symptoms requiring intubation or ventilator support, and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids, interrupt enasidenib until signs and symptoms are no longer severe. Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended. Enasidenib can be resumed when signs and symptoms improve to Grade 2 or lower.

Further information on diagnosis and treatment of IDH differentiation syndrome can be found in the current version of IDH differentiation syndrome guidance documents.

Noninfectious Leukocytosis

Subjects with hematologic malignancies treated with enasidenib may experience rapid myeloid cell proliferation, presenting as an increase in WBC count without evidence of infection or signs of IDH differentiation syndrome.

Blood counts should be assessed for noninfectious leukocytosis (defined as WBC greater than 30 x 10^9/L) prior to the initiation of enasidenib and monitored at a minimum of every 2 weeks for at least the first 3 months during treatment. Any abnormalities should be managed promptly.

Treatment with hydroxyurea should be initiated, as per standard institutional practices. Interrupt enasidenib if leukocytosis is not improved with hydroxyurea, and then resume enasidenib at 100 mg daily when WBC is less than 30 x 10^9/L.

Tumor Lysis Syndrome

Subjects with hematologic malignancies treated with enasidenib may experience tumor lysis syndrome. Manage any abnormalities promptly. If enasidenib-related toxicity is Grade 3 or more, interrupt enasidenib until toxicity resolves.

Gastrointestinal Disorders

Appropriate monitoring and management of GI disorders, such as diarrhea, nausea, and vomiting, is required.

Elevated Serum Bilirubin

Hyperbilirubinemia is induced by enasidenib inhibition of UGT1A1, the enzyme responsible for the metabolism of bilirubin (a condition similar to Gilbert's syndrome).

Patients with Gilbert's syndrome genotype treated with enasidenib experienced earlier onset of bilirubin elevation following treatment initiation, as compared to patients with normal UGT1A1 genotype. With continuing treatment, maximum severity of bilirubin elevation was similar in patients with Gilbert's syndrome and patients with normal UGT1A1 genotype. Reference toxicities of hyperbilirubinemia during AG-221 treatment is described in Section 7.2.1.3, and dose modification due to hyperbilirubinemia Section 7.2.1.2.

7.2.1.4. Initiation of Each AG-221 Treatment Cycle

Subjects will have laboratory assessments performed to evaluate renal, hepatic and hematologic function prior to starting each AG-221 treatment cycle (including Cycle 1).

In order to proceed to the next AG-221 treatment cycle, subjects should manifest recovery of hematologic and non-hematologic toxicities (see Section 7.2.1.3). If the subject does not meet these criteria, the start of the next cycle will be delayed, BSC initiated and the subject evaluated regularly per standard institutional practice and as deemed necessary by the investigator. If there is a delay of more than 28 days (ie, 4 weeks) in the start of the next AG-221 treatment cycle, the Medical Monitor should be consulted for the risks and benefits of continuing AG-221 treatment. Subjects who experience persistent Grade ≥ 3 toxicity that is assessed as possibly or probably related to AG-221 treatment may continue AG-221 treatment if, in the opinion of the investigator and the Medical Monitor, the subject is experiencing clinical benefit from AG-221 treatment.

7.2.2. Azacitidine Treatment

Subjects randomized to the azacitidine treatment option will receive continuous 28-day cycles of azacitidine 75 mg/m^2/day SC for 7 days until the End of Trial, unless they are discontinued from the study treatment for any of the reasons detailed in Section 11.1. In addition, subjects may receive BSC per standard institutional practice and as deemed necessary by the investigator. In the event 2 or fewer doses are missed (eg, skipping weekend dosing per standard institutional practice), dosing should continue so the subject receives the full 7 days of therapy. If 3 or more days are missed, the investigator should contact the Medical Monitor and a decision on dosing will be made on a case-by-case basis. The dose of azacitidine should be calculated on Day 1 of each treatment cycle. The dose during a treatment cycle should not be amended.

7.2.2.1. Dose Modifications for Azacitidine

The first treatment cycle of azacitidine should always be given at 100% of the dose, ie, 75 mg/m^2 SC, regardless of the subject's laboratory values (provided that the subject is allowed to enroll in the study based on the inclusion and exclusion criteria).

Subjects should be monitored for hematologic toxicity and renal toxicity; a delay in starting the next treatment cycle or dose reduction as described below may be necessary. If the dose of azacitidine is modified during the course of the study (see below) and benefit is demonstrated at a dose lower than 75 mg/m^2, that dose should be maintained during subsequent cycles that are given (unless toxicity develops). The investigator should contact the Medical Monitor for guidance on azacitidine dose modification, if needed.

Azacitidine dose modifications due to nonhematological toxicity

Following receipt of any dose of azacitidine, subsequent treatment cycles may be delayed if a certain level of toxicity occurs after the previous dose. Any subject who experiences a non-hematological AE of Grade 3 or 4 that is an escalation from his or her status at baseline (defined in Section 6.2.1) should have azacitidine temporarily discontinued until the toxicity grade returns to less than Grade 3. Azacitidine should be permanently discontinued if the non-hematological toxicity persists as Grade 3 or 4 for more than 21 days, despite the temporary interruption of azacitidine.

Dose modifications due to hematological toxicity

Treatment with azacitidine is associated with anemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles. Complete blood counts should be performed as specified in Table 3 and as needed to monitor response and toxicity.

Recovery is defined as an increase of cell line(s) where hematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (ie, blood count at recovery ≥ Nadir Count + (0.5 x [Baseline count – Nadir count]).

Subjects without reduced baseline blood counts (ie, WBC ≥ 3.0 x 10^9/L, ANC ≥ 1.5 x 10^9/L, and platelets ≥ 75.0 x 10^9/L) prior to the first treatment

If hematological toxicity is observed following azacitidine treatment, the next cycle of azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table.

Following dose modifications, the cycle duration should return to 28 days. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops). A flow diagram for the determination of azacitidine dose adjustment in subjects without reduced baseline blood counts is provided in Appendix L.

Nadir Counts		% Dose in the next course if recovery[a] is not achieved in next 14 days
Absolute Neutrophil Count ($x10^9$/L)	Platelets ($x10^9$/L)	
≤ 1.0	≤ 50.0	50%
> 1.0	> 50.0	100%

[a] Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

Subjects with reduced baseline blood counts (ie, WBC count < 3.0 x 10^9/L or ANC < 1.5 x 10^9/L or platelets < 75.0 x 10^9/L) prior to the first treatment

Following azacitidine treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is less than 50%, or greater than 50% but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC or ANC or platelets is greater than 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced according to the following table:

Bone Marrow Cellularity	% Dose in the next course if recovery[a] is not achieved in next 14 days	
	Recovery ≤ 21 days	Recovery > 21 days
15 – 50%	100%	50%
< 15%	100%	33%

[a] Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

Following dose modifications, the cycle duration should return to 28 days. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops). A flow diagram for the determination of azacitidine dose adjustment in subjects with reduced baseline blood counts is provided in Appendix M.

Renal dysfunction during azacitidine therapy

In previous studies, renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported rarely in subjects treated with intravenous azacitidine in combination with other chemotherapeutic agents. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalemia (serum potassium < 3 mmol/L) developed in 5 subjects with CML treated with azacitidine and

etoposide. If unexplained reductions in serum bicarbonate (< 20 mmol/L) occur, the dose should be reduced by 50% on the next course. Similarly, if unexplained elevations in serum creatinine or BUN to ≥ 2-fold above baseline values and above upper limit normal occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops).

Necrotizing fasciitis during azacitidine therapy

Necrotizing fasciitis, including fatal cases, have been reported in subjects treated with intravenous azacitidine. Azacitidine therapy should be discontinued in subjects who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated.

7.2.3. Low-dose Cytarabine Treatment

Subjects randomized to the LDAC treatment option will receive continuous 28-day cycles of cytarabine 20 mg SC BID for 10 days until the End of Trial, unless they are discontinued from the study treatment for any of the reasons detailed in Section 11.1. In addition, subjects may receive BSC per standard institutional practice and as deemed necessary by the investigator.

Before subjects commence each treatment cycle with LDAC, they should manifest adequate platelet and neutrophil recovery (ie, platelets and neutrophils should return approximately to baseline levels). Individual patients differ considerably regarding their ability to regenerate bone marrow cellularity after chemotherapy. In case of myelotoxicity with unacceptable cytopenia and poor regeneration 2 weeks after the last dose of LDAC, the start of the next treatment cycle can be delayed up to 2 weeks. In the event of prolonged (ie, more than 2 weeks) and severe (ie, Grade 4) neutropenia or thrombocytopenia, complicated by a Grade 4 infection or clinically significant bleeding, the duration of LDAC treatment can be reduced to 7 days, per investigators' discretion. The investigator should contact the Medical Monitor for guidance on LDAC dose modification, if needed.

7.2.4. Intermediate-dose Cytarabine Treatment

Subjects randomized to IDAC treatment option will receive 28-day cycles of cytarabine 0.5 to 1.5 g/m^2/day IV for 3 to 6 days, per standard institutional practice, unless they are discontinued from the study treatment for any of the reasons detailed in Section 11.1. In addition, subjects may receive BSC per standard institutional practice and as deemed necessary by the investigator. Subjects may only receive BSC if IDAC therapy concludes per standard institutional practice. (Note: any local standard regimen different from the above specification will need review and approval by the Medical Monitor.)

The dose of cytarabine should be calculated on Day 1 of each treatment cycle. Before subjects commence each treatment cycle with IDAC, they should manifest adequate platelet and neutrophil recovery as well as recovery of non-hematologic toxicities, per standard institutional practice. Treatment modification of IDAC due to toxicity should be performed according to Cytarabine UK SmPC or per standard institutional practice. The investigator should contact the Medical Monitor for guidance on IDAC modification, if needed.

7.2.5. Best Supportive Care Only Treatment

Subjects randomized to the BSC only treatment option will receive continuous 28-day cycles of BSC per standard institutional practice and as deemed necessary by the investigator until the End of Trial, unless they are discontinued from the study treatment for any of the reasons detailed in Section 11.1. Refer to Section 8 for details about BSC.

7.3. Method of Treatment Assignment

Following review of eligibility, subjects will be assigned by the investigator to one of the CCR treatment options based on the investigator's assessment. Thus the investigator should evaluate prior to randomization whether a subject has any potential contraindications to any of the CCR treatment options based on the azacitidine IB and cytarabine UK SmPC, and which CCR treatment option would be the most suitable for the subject. If, in the investigator's opinion, the subject is contraindicated to receive AG-221 treatment, the subject is not to be randomized.

Following the selection of a CCR treatment option, subjects will be randomized centrally in a 1:1 ratio to receive either the AG-221 treatment or the CCR treatment option pre-selected by the investigator. Randomization will be stratified by prior intensive therapy for AML (yes versus no), primary refractory (yes versus no), and prior allogeneic HSCT for AML (yes versus no).

No crossover between any of the treatment options, including the CCR treatment options, will be permitted during the course of study treatment.

7.4. Packaging and Labeling

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

7.5. Investigational Product Accountability and Disposal

The investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying IP accountability form. The investigator(s) or designee(s) will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene.

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

Investigational product (and comparator product in countries where comparator is designated as NIP) accountability is the responsibility of the investigator and designee. Applicable information such as lot number, tablet or vial count, and expiration date should be collected, as well as information provided by the subject or the caregiver (eg, subject dosing diary).

The investigator(s) or designee(s) is responsible for accounting for all IPs received at the site and issued to and returned by the subject during the course of the study according to applicable regulatory requirements.

Investigational product (and comparator product in countries where comparator is designated as NIP) issued to and returned by the subject will be assessed before drug dispensing for each subsequent treatment cycle and at EOT. This should occur as soon as possible after subjects have completed all scheduled doses of study treatment.

Any unused IP must be returned by a study subject and retained by the investigative site for accountability to be conducted by a Celgene representative (or designee). If any IP is lost or damaged, its disposition should be documented. At the periodic monitoring visits, a Celgene representative (or designee) will conduct IP (and comparator product in countries where comparator is designated as NIP) accountability and address any discrepancies. Upon satisfactory reconciliation of all IPs (and comparator product in countries where comparator is designated as NIP), the Celgene representative (or designee) will authorize for the product to be either returned or destroyed at the site. At the conclusion of the study a final reconciliation will be conducted and all remaining IP will be counted, and reconciled with dispensing records, destruction records, returns and other documents. The Celgene representative (or designee) will ensure that a final drug accountability to the unit dose level (ie, tablet or vial) is conducted. Documentation of this accountability and any discrepancies will be prepared and placed in both the investigator study file and the central clinical study file.

Celgene (or designee) will review with the investigator and relevant site personnel the process for IP (and comparator product in countries where comparator is designated as NIP) return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

If IP is to be destroyed via the site's process, a copy of the site's standard operating procedure (SOP) for drug destruction will be collected by the Sponsor (or designee). Any site without a Sponsor (or designee) approved destruction SOP and process will be required to return IP (and comparator product in countries where comparator is designated as NIP) to Celgene. Any revisions to a site's destruction process must be provided and approved by the Sponsor (or designee) prior to implementation on this protocol.

7.6. Investigational Product Compliance

Study treatment on scheduled clinic visit days will be administered in the clinic by study site personnel after all pre-dose assessments (Section 6.2) have been completed.

- Subjects will self-administer all other AG-221 doses in the Treatment Phase. Documentation of AG-221 dosing during treatment may be recorded in a study specific diary card. AG-221 administration diary cards may be provided by the Sponsor to study site personnel, who will in turn distribute them to study subjects randomized to receive AG-221 treatment. If study specific diary cards are utilized, study site personnel will enter the scheduled daily doses, the number of tablets to be taken each day and any other applicable information, and will review the dosing information with the subject (or legally authorized representative). If study specific diary cards are utilized, subjects (or legally authorized representative) will be asked to record AG-221 dosing information and to bring the diary card and unused tablets in

the bottle (or the bottle if it is empty) with them to all clinic visits. A diary card and tablet compliance check will be performed by study personnel if study specific diary cards are utilized. Diary cards, if utilized, must be saved and kept with the source documentation. Study site personnel will perform an AG-221 administration compliance check and record this information in the subject's source documentation and on the appropriate eCRF page.

- Administration of all other doses of azacitidine, LDAC, IDAC or BSC in the Treatment Phase is per standard institutional practice.

Accurate recording of study treatment administration (including preparation, dosing and any changes in dosage administration such as interruption or reduction in dosing due to an AE) will be made in the appropriate section of the subject's eCRF and source documents.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All prior and concomitant medications (prescription and non-prescription) taken and treatment procedures received from the 4-week period (ie, 28 days) prior to starting study treatment up to 28 days after the last study treatment must be recorded on the appropriate eCRF page(s). Particularly, all prior anti-cancer treatments should be recorded regardless of discontinuation date of treatment.

For information regarding other drugs that may interact with study treatment and affect its metabolism, [redacted] or excretion, see the respective IBs and/or Cytarabine UK SmPC.

8.1. Permitted Concomitant Medications and Procedures

Supportive care may be used per standard institutional practice and as deemed necessary by the investigator. Supportive care includes prophylactic antibiotics, antifungal and/or antiviral agents, analgesics, antiemetics, antipyretics, RBC transfusions (packed RBC or whole blood), single donor or pooled donor platelet transfusions and nutritional support.

The use of erythropoiesis stimulating agents (ESAs) is permitted according to the American Society of Clinical Oncology Guidelines (Rizzo, 2010).

The use of myeloid growth factors (granulocyte-colony stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection.

Treatment with hydroxyurea is allowed after the start of study treatment for the control of leukocytosis and/or if subjects experience IDH Differentiation Syndrome (Section 7.2.1.3) during the course of study treatment. However, hydroxyurea should not be given within the 72 hours prior to and after azacitidine administration.

Steroids are allowed for the treatment of IDH Differentiation Syndrome, if warranted, as standard of care. The use of chronic low-dose steroids to treat an underlying medical condition that is not a malignancy is permitted during the course of study treatment.

It is recommended that an antiemetic medication such as a serotonin 5-HT_3 receptor antagonist (eg, ondansetron) be taken 30 minutes prior to azacitidine administration during Cycle 1. If nausea/vomiting is not significant, further antiemetic prophylaxis may not be needed. Pretreatment or posttreatment with a serotonin 5-HT_3 receptor antagonists, or other locally available and appropriate antiemetic medication, will be considered concomitant treatment and should be recorded on the appropriate subject's eCRF. Treatment with antidiarrheal medications is recommended at the first sign of diarrhea. Premedication with antidiarrheal medication for subsequent doses of azacitidine may be appropriate. Pretreatment and posttreatment with antidiarrheal medication will be considered concomitant treatment and should be recorded on the appropriate subject's eCRF.

8.2. Prohibited Concomitant Medications and Procedures

Systemic anti-cancer therapy (excluding hydroxyurea) is not permitted during the course of study treatment. Hydroxyurea is allowed after the start of study treatment for the control of leukocytosis and/or if subjects experience IDH Differentiation Syndrome during the course of study treatment.

If AML therapy other than the study-prescribed treatment is required for treatment of the subject's AML disease, the subject should be discontinued from study treatment.

The following therapies are not permitted during the course of azacitidine treatment:

- Oral retinoids (topical retinoids are permitted)

The following therapies are not permitted during the course of AG-221 treatment:

- Corticosteroids, with the exception of topical cutaneous, ophthalmic, nasal, and inhalational steroids. Note that short course steroid therapy will be permitted to treat co-morbidities such as IDH Differentiation Syndrome. The use of a stable dose of oral steroids post HSCT and/or topical steroids for ongoing skin GVHD is permitted.
- The following medications that are known to prolong QT interval: amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, escitalopram, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sevoflurane, sotalol, sparfloxacin, terfenadine, thioridazine, or vandetanib
- Sensitive CYP substrate medications that have a narrow therapeutic range: paclitaxel and docetaxel (CYP2C8), phenytoin (CYP2C9), S-mephenytoin (CYP2C19), thioridazine (CYP2D6), theophylline and tizanidine (CYP1A2)
- The BCRP transporter-sensitive substrate rosuvastatin

The following therapies are not permitted during the course of cytarabine treatment:

- 5-Flurocytosine (the antifungal efficacy of 5-Fluorocytosine has been shown to be abolished during cytarabine therapy)
- Live or live-attenuated vaccines (Administration of these vaccines may result in serious or fatal infections. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.)

8.3. Restricted Concomitant Medications and Procedures

The following therapies are restricted during the course of AG-221 treatment:

- Coadministration of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2B6, CYP3A4, and CYP1A2 substrates other than those listed in Section 8.2 should be used only if medically necessary (refer to Appendix N for a list of CYP substrates)
- Coadministration of P-gp or BCRP substrates, OAT, OATP1B and OCT2 substrates other than those listed in Section 8.2 should be used only if medically necessary (refer to Appendix O for a list of transporter substrates)
- Given the solubility profile of AG-221, the exposure can be much lower for subjects with elevated gastric pH. Thus antacids, H2 blockers, or proton pump inhibitors should be used only if medically necessary and with at least 4 hours of elapsed time after AG-221 administration.

- As an inhibitor of UGT1A1, AG-221 may slow down the metabolism of drugs that are substrates for UGT1A1, such as irinotecan, ezetimibe, raloxifene, and raltegravir. If this applies, especially in subjects who develop hyperbilirubinemia, it might be necessary to lower the doses for UGT1A1 substrates or switch to alternate therapies, or otherwise monitor for AEs associated with the respective products.

8.4. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL CONSIDERATIONS

The sections below provide an overview of the proposed statistical considerations and analyses. The final statistical analysis methods will be documented in detail in the statistical analysis plan (SAP).

9.1. Overview

This is an international, multicenter, open-label, randomized, Phase 3 study comparing the efficacy and safety of AG-221 versus CCRs in subjects 60 years or older with AML refractory to or relapsed after second- or third-line AML therapy and positive for an IDH2 mutation.

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

All statistical analyses specified in this protocol will be conducted using SAS® Version 9.2 or higher unless otherwise specified.

9.2. Study Population Definitions

9.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population includes all subjects who are randomized to treatment, regardless of whether they received treatment or not.

9.2.2. Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all subjects who have met all eligibility criteria and experienced no major protocol deviations during the study, received at least one dose of study treatment and had at least one treatment response assessment performed. This definition will be further clarified and detailed in the final SAP prior to database lock.

9.2.3. Safety Population

The safety population includes all randomized subjects who received at least 1 dose of study treatment. Because BSC only treatment may consist of blood products or antibiotics, etc, administered only as needed, subjects who are randomized to the BSC only treatment option will be included in the safety population if they have had at least 1 post-randomization assessment. The safety population will be used for all safety analyses. Subjects will be analyzed according to the treatment actually received.

[redacted]

[redacted]

9.3. Sample Size and Power Considerations

The equality of overall survival curves will be compared between the AG-221 and CCR treatment arms using a stratified log-rank test. Subjects will be randomized to receive AG-221 treatment or a CCR treatment option pre-selected by the investigator in a 1:1 ratio. Assuming a median OS of 5.6 months in the CCR treatment arm (Roboz, 2014), a median OS of 8 months in the AG-221 treatment arm (42.9% improvement), and a drop-out rate of approximately 9%, this design requires 250 deaths and 316 subjects (158 per treatment arm) to be randomized in order to achieve 80% power to detect a constant hazard ratio (HR) of 0.7 and demonstrate a statistically significant difference in OS at a Type I error rate of 0.05 (two-sided). It is assumed that the OS distribution is exponential with a constant failure rate and that accrual rate is 3 subjects per month for the first 12 months and 9 subjects per month afterwards. The interim analysis for superiority will be conducted at 65% information (ie, 163 deaths) based on Lan-DeMets version of the O'Brien-Fleming alpha spending function.

[redacted]

9.4. Background and Demographic Characteristics

Demographic and baseline disease characteristics will be summarized by treatment group for the ITT, mITT and safety populations. Subjects' age, height, weight, and continuous baseline characteristics will be summarized using descriptive statistics (N, mean, SDev, median, minimum, maximum), while age group, gender, race and other categorical variables will be provided using frequency tabulations (count, percent) by treatment group.

9.5. Subject Disposition

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

9.6. Efficacy Analysis

All efficacy analyses will be performed on the ITT population. Key secondary efficacy analysis will be performed on the mITT population as supportive evidence and to assess the robustness of the efficacy findings. Subjects will be analyzed according to randomized treatment group. Refer to Section 2 for the primary and secondary efficacy endpoints, respectively.

In order to perform hypothesis testing on multiple endpoints while controlling the overall Type I error rate, a closed, sequential testing approach is proposed with the endpoints to be tested in a pre-specified order. The primary efficacy endpoint of OS will be tested first at a two-sided significance level of 0.05. If superiority of AG-221 is demonstrated in OS, then each of the key secondary endpoints of overall response rate (ORR) and event-free survival (EFS), in the pre-

specified priority order will be tested, each at a two-sided 0.05 significance level once the superiority of the previous endpoint is established.

9.6.1. Primary Efficacy Analysis

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

The analysis of the primary endpoint will use the stratified log-rank test in the ITT population. This test will provide the pivotal p-value summarizing the comparison of the two OS curves of AG-221 and CCRs. Subjects will be analyzed as they were randomized, regardless of the actual treatment received. The stratification used for the log-rank test will be the same stratification used for randomization. The corresponding stratified Cox proportional hazards regression model with treatment as the only term will be used to estimate the hazard ratio and a 95% confidence interval.

The assumption of proportional hazards will be tested by a time-dependent Cox model with the interaction of treatment and time. A significant interaction indicates that the proportional hazard assumption is violated. Under such circumstance, restricted mean survival time and piecewise Cox regression will be adopted to estimate treatment effect. Generalized Wilcoxon test will be utilized as a sensitivity analysis when treatment difference occurs early rather than late during the Follow-up period.

In order to assess the impact of subsequent enasidenib treatment in the CCR arm, sensitivity analyses of OS will be conducted following ICH E9 (R1) addendum, in which strategies to address intercurrent events are described. To be specific, Hypothetical Strategy, eg, regression-based imputation method (Luo, 2016) and Rank Preserve Structure Failure Time model (Robins, 1991), Principal Stratum Strategy, eg, Inverse Probability of Censoring Weighted method (Robins, 2000), and While on Treatment Strategy to censor subjects at the time of crossover will be adopted to provide supporting evidence when appropriate. In addition, to assess the impact of subsequent transplantation, a sensitivity analysis of OS will be conducted in which subjects who have subsequent transplantation will be censored at the time of transplantation after study treatments.

9.6.2. Secondary Efficacy Analyses

The time-to-event secondary efficacy variables will be analyzed similarly to the primary efficacy variable with or without stratification when appropriate. Kaplan-Meier (KM) methods will be used to estimate time-to-event curves, unless otherwise specified. Counts and percentages will be used to describe categorical secondary variables.

9.6.2.1. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints include ORR and EFS assessed by a blinded IRAC according to modified IWG AML response criteria (Appendix F). Overall response rate will be compared by Cochran-Mantel-Haenszel test.

Overall response rate is defined as the rate of morphologic leukemia-free state (MLFS) + CR + CRi + CRp + PR according to modified IWG AML response criteria (Appendix F).

Event-free survival is defined as the interval from the date of randomization to the date of documented morphologic relapse after CR/CRi/CRp, PD or death from any cause, whichever occurs first. Subjects who are alive without any of these events will be censored at the date of their last response assessment.

9.6.2.2. Additional Secondary Efficacy Analyses

The other secondary endpoints include duration of response, time to response, rates of overall remission, CR and HI assessed by an IRAC according to modified IWG AML response criteria (Appendix F) and IWG MDS HI criteria (Appendix H), treatment mortality at 30 and 60 days, one-year survival, rate of HSCT and time to treatment failure. The definitions of these additional secondary efficacy endpoints are listed below and in Section 2.

Duration of response is defined as time from first documented MLFS/CR/CRi/CRp/ PR to documented morphologic relapse after CR/CRi/CRp/ PD or death due to any cause, whichever occurs first. Subjects without morphologic relapse, PD or death due to any cause will be censored at the date of the last response assessment.

Time to response is defined as time from randomization to first documented MLFS/CR/CRi/CRp/ /PR. Subjects without a MLFS/CR/CRi/CRp/ PR will be censored at the date of the last response assessment.

Treatment mortality at 30 and 60 days is defined as rate of death from any cause within 30 or 60 days of initiation of study treatment.

One-year survival is defined as the probability of survival at 1 year from randomization.

Overall remission rate is defined as rate of CR + CRi + CRp according to modified IWG AML response criteria (Appendix F).

Complete remission rate is defined as rate of CR according to modified IWG AML response criteria (Appendix F).

Hematologic improvement rate is defined as rate of neutrophil response (hematologic improvement neutrophil response [HI-N]) + platelet response (hematologic improvement platelet response [HI-P]) + erythroid response (hematologic improvement erythroid response [HI-E]) according to IWG MDS HI criteria (Appendix H).

Rate of HSCT is defined as rate of bridge-to-HSCT through study treatment.

Time to treatment failure is defined as time from randomization to discontinuation of study treatment due to any cause.

The rate of CR/CR with partial hematologic recovery (CRh; Appendix F) and duration of CR/CRh will be analyzed using the statistical methods mentioned above or other statistical methods as appropriate. Note: CRh is not available for the investigator's assessment and will be assessed by the Sponsor only and based on laboratory dataset.

9.7. Safety Analysis

All safety analyses will be performed on the safety population.

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Treatment-emergent AEs leading to death, TEAEs leading to discontinuation from treatment, CTCAE Grade 3 or Grade 4 TEAEs, TEAEs any CTCAE grade, TEAEs related to study treatment and serious TEAEs will be summarized separately.

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

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

Electrocardiograms will be analyzed for QTc intervals, QTc > 480 and > 500, increase > 30 and > 60 msec.

9.8. Interim Analysis

The interim analysis for superiority will be performed when approximately 65% of the expected number of deaths (ie, 163 deaths) have been reported. The interim efficacy analysis will be performed by an independent third party and the results will be kept strictly confidential in order to maintain the integrity of the study. The interim results will be provided to the DMC who will review and give advice to the Sponsor regarding the study conduct. The analysis results will not be disseminated among investigators and those directly involved with the study conduct.

The Type I error rate will be controlled at the overall one-sided 0.025 level by using an O'Brien-Fleming monitoring boundary with a Lan-DeMets alpha spending function. The decision rules are as follows:

- 65% of expected events

  Stop for superiority if one-sided p-value ≤ 0.0055 (HR ≤ 0.6715)

- 100% of expected events

  Claim success if one-sided p-value ≤ 0.0233 (HR ≤ 0.7775)

The actual levels used will depend on the actual number of events observed at the interim and the final analyses. Based on the study assumptions, the superiority interim is projected to occur approximately 37 months after the first subject is randomized and 256 subjects have been accrued.

At the time of the interim analysis, the overall death rate will be evaluated relative to the study assumptions and enrollment into the study may be increased to ensure that the required number of 250 deaths can be reached in a reasonable time period.

9.9. Other Topics

9.9.1. Data Monitoring Committee

An external DMC will be convened that will include medical hematologists/oncologists with experience in treating subjects with AML and a statistician, all of whom are not otherwise involved in the study conduct. During the course of the study, the DMC will review the safety data regularly as well as safety and efficacy data in accordance with the guidelines for the preplanned interim analysis. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to the DMC members for each scheduled meeting. Operational details for the DMC will be detailed in the DMC charter.

9.9.2. Steering Committee

The conduct of this trial will be overseen by a steering committee, presided over by the coordinating Principal Investigator and if possible the representative Regional Investigators from countries participating in this study. The steering committee will serve in an advisory capacity to the Sponsor. Operational details for the steering committee will be detailed in a separate steering committee charter.

Note: The steering committee is separate from the DMC.

9.9.3. Health-Related Quality-of-Life

Two instruments, the EORTC QLQ-C30 and EuroQoL Group EQ-5D, will be used for HRQoL.

Scoring for EORTC QLQ-C30 and EQ-5D, and methods to address missing values will be accomplished according to directions provided by the instrument developers. Detailed analysis plans will be described in the subject-reported outcome statistical plan.

[redacted]

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. See Section 7.2 for the definition of overdose. Any sequela of an accidental or intentional overdose of study treatment should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for overdose of IP. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

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

All AEs will be recorded by the investigator from the time the subject signs informed consent until 28 days after the last dose of IP or until the EOT visit, whichever is longer, as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified investigator will evaluate all AEs as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

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

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

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

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

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

10.2.2. Severity/Intensity

For both AEs and SAEs, the investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03);

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

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

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

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

10.2.3. Causality

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

Not suspected:	a causal relationship of the AE to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the AE.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

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

10.2.4. Duration

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

10.2.5. Action Taken

The investigator will report the action taken with study treatment as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

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

10.3. Abnormal Laboratory Values

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

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

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

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 4 months of the subject's last dose of IP (6 months following the last dose of cytarabine), are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

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

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

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant while the male subject is on IP, or within 4 months of the male subject's last dose of IP (6 months following the last dose of cytarabine; 6 months following the last dose of azacitidine in Canada), the male subject taking IP should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Where applicable, the IP may need to be discontinued in the male subject, but may be resumed later at the discretion of the investigator and the Medical Monitor.

10.5. Reporting of Serious Adverse Events

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

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last study treatment or

until the EOT visit, whichever is longer) or any SAE made known to the investigator at anytime thereafter that are suspected of being related to IP. Serious AEs occurring prior to treatment (after signing the ICF) will be captured.

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

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

10.5.1. Safety Queries

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

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to AG-221 or azacitidine based on AG-221 (enasidenib) IB or Azacitidine IB, respectively.

In the US, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

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

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP, specifically, the Cytarabine UK SmPC.

Events of disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as AEs and will not be reported as expedited safety reports to regulatory authorities.

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

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- In Japan, measures taken in foreign countries to ensure subject safety, study reports that indicate potential risk of cancer, etc, or biannual SAE report according to the local regulations.

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

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information.)

Celgene Drug Safety Contact Information:

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

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from study treatment:

- Adverse event
- Progressive disease (Appendix F)
- Withdrawal by subject from study treatment
- Death
- Lost to follow-up
- Allogeneic HSCT
- Pregnancy
- Other (to be specified on the eCRF)

Although progressive disease is considered a sufficient reason for discontinuing a subject from study treatment, the investigator may consider continuing study treatment until the investigator has alternative therapies (eg, allogeneic HSCT) and/or considers study treatment to be no longer beneficial to the subject, or the rapidity of change of disease state renders it unacceptable for further study treatment in the judgment of the investigator.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject for progressive disease, or any other reason if not listed above, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion. The reason for discontinuation of study treatment should be recorded in the eCRF and in the source documents.

Discontinued subjects will not be replaced.

11.2. Study Discontinuation

Discontinuation from study treatment should be considered distinct from discontinuation from the study. All subjects discontinued from study treatment for any reason other than withdrawal of consent for follow-up, death or lost to follow-up will be followed in the Follow-up Phase of the study (Section 6.3). Every attempt should be made to collect all data during the Follow-up Phase unless subjects discontinue from the study.

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
  - IDH2 mutation negative
  - Other

- Adverse event
- Withdrawal by subject from study
- Death
- Lost to follow-up
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

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

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

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

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

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

13.2. Investigator Responsibilities

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

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

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

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

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide investigators with a summary of the results that is written for the lay person. The investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

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

13.4. Confidentiality

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

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

13.5. Protocol Amendments

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

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

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

Investigational product can only be supplied to an investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has

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

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

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

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

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

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

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

13.8. Termination of the Study

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

The Sponsor may end the trial when all key endpoints and objectives of the study have been analyzed, and the availability of a roll-over or extension protocol exists into which any subjects who remain on study may be consented and continue to receive access to AG-221. Such a protocol would be written for a compound that would not yet be commercially available.

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

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;

- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

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

14.2. Data Management

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

14.3. Record Retention

Essential documents must be retained by the investigator according to the period of time outlined in the clinical trial agreement. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

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

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

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the investigator and the staff at a study initiation visit and/or at an investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

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

15.2. Audits and Inspections

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

The investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The investigator should make every effort to be available for the audits and/or inspections. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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18. APPENDICES

Appendix A: Table of Abbreviations

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACS	Acute coronary syndrome
AE	Adverse event
[redacted]	
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
BCRP	Breast cancer resistance protein
β-hCG	β-subunit of human chorionic gonadotropin
BID	Twice a day
BP	Blood pressure
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BSA	Body surface area
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CCR	Conventional care regimen
CI	Confidence interval
CML	Chronic myelogenous leukemia
CNS	Central nervous system
CO_2	Carbon dioxide
CR	Morphologic complete remission
CRh	Morphologic complete remission with partial hematologic recovery
CRi	Morphologic complete remission with incomplete neutrophil recovery
CRp	Morphologic complete remission with incomplete platelet recovery

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome
DNA	Deoxyribonucleic acid
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
EFS	Event-free survival
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
[redacted]	
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony-stimulating factor
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
[redacted]	

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
HDPE	High density polyethylene
[redacted]	
HI	Hematologic improvement
HI-E	Hematologic improvement erythroid response
HI-N	Hematologic improvement neutrophil response
HI-P	Hematologic improvement platelet response
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related Quality-of-Life
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IDAC	Intermediate-dose cytarabine
IDH	Isocitrate dehydrogenase
[redacted]	
IDH2	Isocitrate dehydrogenase 2
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRAC	Independent Response Assessment Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenously
IVRS	Interactive voice response system
IWG	International Working Group
KM	Kaplan-Meier
[redacted]	
LDAC	Low-dose cytarabine
LDL-C	Low-density lipoprotein cholesterol

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndromes
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
[redacted]	
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
mITT	Modified intent-to-treat
MLFS	Morphologic leukemia-free state
MPN	Myeloproliferative neoplasm
[redacted]	
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	
NIP	Non-investigation product
NYHA	New York Heart Association
OAT	Organic anion transporter
[redacted]	
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
P-gp	P-glycoprotein
[redacted]	

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PO	Orally
PR	Partial remission
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once a day
QTc	Heart rate-corrected QT
QTcF	QTc with Fridericia's correction
RBC	Red blood cell
[redacted]	
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Stable disease
SDev	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	
UDP	Uridine diphosphate
[redacted]	
UGT1A1	UDP-glucuronosyltransferase 1 family, polypeptide A1
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WBC	White blood cell

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
WHO	World Health Organization

Appendix B: World Health Organization Classification of Acute Myeloid Leukemia

Acute myeloid leukemia with recurrent genetic abnormalities

- Acute myeloid leukemia with t(8;21)(q22;q22); (RUNX1-RUNX1T1)
- Acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); (CBFB-MYH11)
- Acute promyelocytic leukemia with t(15;17)(q22;q12); (PML-RARA)
- Acute myeloid leukemia with t(9;11)(p22;q23); MLLT3-MLL
- Acute myeloid leukemia with t(6;9)(p23q34); DEK-NUP214
- Acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q26.2); RPN1-EVI1
- Acute myeloid leukemia (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
- Acute myeloid leukemia with gene mutations

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasma

Acute myeloid leukemia, not otherwise categorized

- Acute myeloid leukemia with minimal differentiation
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic and monocytic leukemia
- Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Source: Swerdlow, 2008.

Appendix C: Acute Myeloid Leukemia Risk Status

Risk Status	Cytogenetics	Molecular Abnormalities [a]
Better-risk	inv(16)[b, c] t(16;16)[b] t(8;21)[b] t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 t(9;11) Other non-defined	t(8;21), inv(16), t(16;16): with c-KIT [d] mutation
Poor-risk	Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[e]	Normal cytogenetics: with FLT3-ITD mutation [f]

[a] The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

[b] Other cytogenetic abnormalities in addition to these finding do not alter risk status.

[c] Paschka P, Du J, Schlenk RF, Gaidzik VI, Bullinger L, Corbacioglu A, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 2013; 121:170-177.

[d] Emerging data indicates the presence of c-KIT mutation in subjects with t(8;21), and to a lesser extent, inv(16), confers a high risk of relapse. These subjects should be considered for clinical trials, if available.

[e] For Philadelphia+ acute myeloid leukemia (AML) t(9;22), manage as myeloid blast crisis in chronic myeloid leukemia (CML), with addition of tyrosine kinase inhibitors. These subjects are excluded from study entry.

[f] FLT3-ITD mutations are considered to confer a significant poor outcome in subjects with normal karyotype, and these subjects should be considered for clinical trials where available. There is controversy as whether FLT3-TKD mutations carry equally poor prognosis

Source:

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Acute Myeloid Leukemia. National Comprehensive Cancer Network website. Available at http://www nccn.org/professionals/physician_gls/PDF/aml.pdf. Accessed 05 Aug 2015.

Appendix D: Eastern Cooperative Oncology Group (ECOG) Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status	
Grade	**ECOG**
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 house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Source: Oken, 1982.

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

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

Source: American Heart Association, 1994.

Appendix F: International Working Group Acute Myeloid Leukemia Response Criteria

Hematologic Response According to modified IWG Criteria for AML	
Category	**Definition**
Morphologic Complete Remission (CR)	Defined as less than 5% blasts in a BM aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There should be no blasts with Auer rods and absence of extramedullary disease. Plus, all the following conditions should be met: • ANC ≥ 1 x 10^9/L (1,000/μL) • Platelet count ≥ 100 x 10^9/L (100,000/μL) • Independent of red cell transfusions for ≥ 1 week immediately before each response assessment
Morphologic Complete Remission with Incomplete Neutrophil Recovery (CRi) [a]	Defined as all criteria of CR except the following: • ANC < 1 x 10^9/L (1,000/μL)
Morphologic Complete Remission with Incomplete Platelet Recovery (CRp) [a]	Defined as all criteria of CR except the following: • Platelet count < 100 x 10^9/L (100,000/μL)
Morphologic Complete Remission with Partial Hematologic Recovery (CRh) [a]	Defined as all criteria of CR except the following: • ANC > 0.5 x 10^9/L (500/μL); and • Platelet count > 50 x 10^9/L (50,000/μL)
Morphologic Leukemia-free State (MLFS)	Defined as less than 5% blasts in a BM aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There should be no blasts with Auer rods and absence of extramedullary disease
Partial Remission (PR)	Defined as all hematologic criteria of CR with a > 50% decrease in the percentage of BM blasts to 5% to 25% (a blast count value of < 5% may also be considered a partial remission if Auer rods are present) [b]
Cytogenetic Complete Remission (CRc)	Defined as CR/CRi/CRp with a reversion to a normal karyotype in cases with an abnormal karyotype at baseline, based on evaluating ≥ 20 metaphase BM cells
Morphologic Relapse after CR/CRi/CRp [a]	Defined as one of the following conditions: • Reappearance of ≥ 5% blasts in the BM not attributable to any other cause (eg, BM regeneration after consolidation therapy); or • Development of extramedullary disease
Not evaluable (NE) [a]	Defined as without a posttreatment response assessment
Stable Disease (SD) [a]	Defined as failure to meet any of the above criteria and not meeting the criteria of progressive disease (see below)
Progressive Disease (PD) [a]	Defined as one of the following conditions: • For subjects with 5 to 70% BM blasts at baseline: a > 50% increase of **BM blast count percentage** from baseline to ≥ 20%; or • For subjects with > 70% BM blasts at baseline: a doubling of **absolute blast count in peripheral blood** from baseline to ≥ 10 x 10^9/L (10,000/μL); or • Development of new extramedullary disease since last response assessment Progressive disease is to be confirmed by 2 consecutive response assessments separated by at least 1 month. The date of progressive disease is defined as the first date that one of three conditions listed above was met.

AML = Acute Myeloid Leukemia; ANC= Absolute Neutrophil Count; BM= Bone Marrow; IWG= International Working Group.

[a] Modification to IWG response criteria. Note: CRh is not available for the investigator's assessment and will be assessed by the Sponsor only and based on laboratory dataset.

[b] If the pre-treatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pre-treatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%.

Notes: Deletions to the IWG response criteria are not shown.

Source: Cheson, 2003.

Appendix G: Definitions of Prior Line of AML Therapy

A line of AML therapy is defined as cytotoxic chemotherapy or low-intensity therapy, single agent or in combination, delivered with the intent to induce remission and/or prolong survival.

If remission is not induced by the first cycle (eg, cytarabine 100-200 mg/m^2 continuous infusion for 7 days), the second cycle is modified (eg, cytarabine 1 to 3 g/m^2 every 12 hours for 3 to 7 days) with the intent to induce remission, then the subject has received two different lines of AML therapy. Treatment modifications with the intent to manage toxicity are not counted as separate lines.

The line used for re-induction for first relapse is also regarded as a second line even if the same drugs are given at the same doses as for the first remission induction, since the disease characteristics have changed from diagnosis to relapse.

Post-remission strategies (regimens) such as consolidation or maintenance are not counted as separate lines.

Transplantation is considered as a line if given with the intent to induce remission. However, transplantation as a post-remission strategy is not considered a separate line as it is regarded as consolidation.

Hydroxyurea is not counted as a separate line.

Note that, for subjects having AML secondary to prior higher risk (Intermediate-2 or High risk according to the International Prognostic Scoring System [see below]) MDS treated with a hypomethylating agent [eg, azacitidine or decitabine], the hypomethylating therapy can be counted as a line if there is disease progression to AML during or shortly (eg, within 60 days) after the hypomethylating therapy.

International Prognostic Scoring System for MDS					
	Score Value				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone Marrow Blasts (%)	< 5	5-10	-	11-20	21-30
Karyotype[a]	Good	Intermediate	Poor	-	-
Cytopenias[b]	0 or 1	2 or 3	-	-	-

[a] Good: normal, -Y, del(5q), del(20q); Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate: other abnormalities.

[b] Defined as: Hemoglobin < 100 g/L, absolute neutrophil count < 1.5 x 10^9/L, and platelet count < 100 x 10^9/L.

Note: Scores for risk groups are as follows: Low = 0; INT-1 = 0.5-1.0; INT-2 = 1.5-2.0; and High: ≥ 2.5.

Source: Greenberg, 1997.

Appendix H: Hematologic Improvement According to the International Working Group for Myelodysplastic Syndromes

Hematologic Improvement According to IWG Criteria	
Hematologic improvement [a]	**Response criteria (responses must last at least 8 week)**[b]
Erythroid Response (HI-E) (pre-treatment, < 11 g/dL)	• Hemoglobin increase by ≥ 1.5 g/dL • Relevant Reduction in units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 week compared with the pretreatment transfusion number in the previous 8 week Note: Only RBC transfusions given for a hemoglobin of ≤ 9.0 g/dL on treatment will count in the RBC transfusion response evaluation [b]
Platelet Response (HI-P) (pre-treatment, < 100 X 10^9/L)	• Absolute increase of ≥ 30 X 10^9/L for subjects starting with > 20 X 10^9/L platelets • Increase from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100% [b]
Neutrophil Response (HI-N) (pre-treatment, < 1.0 X 10^9/L)	• At least 100% increase and an absolute increase > 0.5 X 10^9/L[b]
Progression or Relapse After HI [c]	At least 1 of the following: • At least 50% decrease from maximum response levels in granulocytes or platelets • Reduction in hemoglobin by ≥ 1.5 g/dL • Transfusion dependence

HI-E = hematologic improvement erythroid response; HI-N = hematologic improvement neutrophil response; HI-P = hematologic improvement platelet response; IWG = International Working Group; RBC = red blood cell.

[a] Pre-treatment counts averages of at least 2 measurements (not influenced by transfusions, ie, no RBC transfusions for 2 weeks and no platelet transfusions for 1 week) ≥ 1 week apart (modification).
[b] Modification to IWG (2000) response criteria.
[c] In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Note: Deletions to the IWG response criteria are not shown. To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: Cheson, 2006.

Appendix I: European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (Version 3.0)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Appendix I: European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (Version 3.0) (Continued)

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix J: EQ-5D-5L Health Questionnaire (English Version for the UK)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

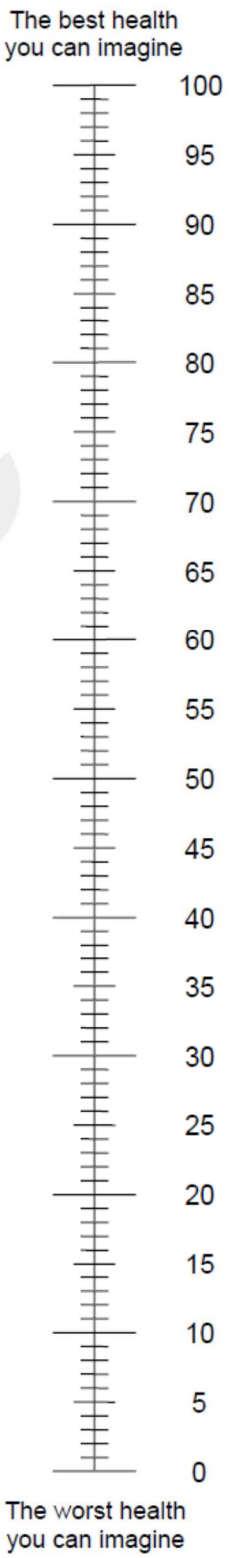
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

Appendix J: EQ-5D-5L Health Questionnaire (English Version for the UK) (Continued)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix K: Subcutaneous Preparation and Administration of Azacitidine

Recommendations for Safe Handling

Azacitidine is a cytotoxic medicinal product and, as with other potentially toxic compounds, caution should be exercised when handling and preparing azacitidine suspensions. Procedures for proper handling and disposal of anticancer medicinal products should be applied. If reconstituted azacitidine comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

Overview of Two Methods for Preparing Injection

Azacitidine degrades rapidly at room temperature following reconstitution; therefore the azacitidine suspension should be prepared immediately before use (Method A) or should be refrigerated immediately after reconstitution (Method B).

Method A: The total time from reconstitution to administration should be no greater than 45 minutes (60 minutes in the US):

1. Reconstitute (see next page for instructions). Record time of reconstitution.
2. Prior to administration to the subject, the nurse/doctor must check the time of reconstitution. If elapsed time is greater than 45 minutes (60 minutes in the US), the dose should be discarded appropriately and a new dose prepared.
3. Nurse or doctor must administer dose to subject and record time of administration.

Method B: If the product must be reconstituted in advance of the dose, it should be prepared as follows:

1. Reconstitute. Record time of reconstitution.
2. Place in refrigerator (2°C to 8°C [36°F to 46°F]) immediately. Record time of placement in refrigerator. If the suspension is prepared using water for injections that has not been refrigerated (2°C to 8°C [36°F to 46°F]), the suspension may be held under refrigerated conditions for a maximum of 8 hours (22 hours if the suspension is prepared using refrigerated water for injections).
3. When ready to administer, remove from refrigerator. Record time. If elapsed time held in refrigerator is over the maximum hours as defined above, the suspension should be discarded appropriately and a new dose prepared.
4. The syringe filled with reconstituted suspension should be allowed, up to 30 minutes prior to administration, to reach a temperature of approximately 20°C to 25°C (68°F to 77°F).
5. Prior to administration to the subject, the nurse/doctor must check the time of removal from the refrigerator. If elapsed time is more than 30 minutes, the dose should be discarded appropriately and a new dose prepared.
6. Nurse or doctor must administer dose to subject and record time of administration.

Appendix K: Subcutaneous Preparation and Administration of Azacitidine (Continued)

Preparing the suspension for subcutaneous administration:

1. Assemble the following supplies:
   - Vial(s) of azacitidine;
   - Vial(s) of sterile water for injection;
   - Nonsterile surgical gloves;
   - Alcohol wipes;
   - 5 mL syringe(s) with 18-gauge needle(s); and
   - Additional 25-gauge needle(s) for subcutaneous injection.
2. Document the sequence number of vial(s) on the source document.
3. Wash and dry hands and put on gloves.
4. Remove the syringe from its protective wrapper by peeling back the paper label.
5. Remove the plastic cover from the sterile water vial and use an alcohol wipe to clean the rubber top. Do not touch the rubber top after it is cleaned.
6. Remove the plastic cover from the azacitidine vial, shake the vial to break up the lyophilized cake, and use a fresh alcohol wipe to clean the rubber top. Do not touch the rubber top after it is cleaned.
7. Remove the plastic cap from the 18-gauge needle and attach to the syringe. Never touch the needle.
8. Pull the plunger back to the 4 mL mark to draw air into the syringe.
9. Insert the needle through the rubber top of the sterile water vial and push the plunger all the way in.
10. Leave the needle/syringe in the vial and turn the vial upside down. Make sure the needle tip is below the level of the liquid. Pull the plunger back to draw 4 mL of sterile water into the syringe, making sure to purge any air trapped within the syringe.
11. Pull the needle/syringe out of the vial and set the vial down.
12. Insert the needle of the syringe with sterile water through the rubber top of the azacitidine vial and slowly inject the 4 mL of sterile water into the vial. Document the preparation and administration time interval. The preparation time begins when the sterile water is added to the vial of azacitidine. Record the exact time in the pharmacy and other applicable records.

Appendix K: Subcutaneous Preparation and Administration of Azacitidine (Continued)

13. Remove the syringe and needle. The vial should be vigorously shaken until a uniform cloudy suspension is achieved. The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates. Do not filter the suspension after reconstitution since this could remove the active substance. It must be taken into account that filters are present in some adapters, spikes, and closed systems; therefore such systems should not be used for administration of the drug after reconstitution. After reconstitution each milliliter of suspension will contain 25 mg of azacitidine (100 mg/4 mL).
14. Using an alcohol wipe, clean the rubber top and insert a new needle and syringe. Turn the vial upside down. Make sure the needle tip is below the level of the liquid. Pull the plunger back to withdraw the amount of drug required for the proper dose, making sure to purge any air trapped within the syringe.
15. Pull the needle/syringe out of the vial. Properly dispose of the needle according to local pharmacy standard operating procedures and other applicable guidelines.
16. Remove a fresh subcutaneous needle (recommended 25-gauge) for injection from its paper wrapper and firmly attach it to the syringe, being careful to not touch the tip of the syringe.
17. If needed (doses over 100 mg) repeat all the above steps for preparation of the suspension. For doses greater than 100 mg (4 mL), the dose should be equally divided into 2 syringes (eg, dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe). All syringes should be prepared prior to starting administration.

The contents of the dosing syringe must be re-suspended immediately prior to administration. The temperature of the suspension at the time of injection should be approximately 20°C to 25°C (68°F to 77°F). To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. The product should be discarded if it contains large particles or agglomerates. Azacitidine is supplied in single-use vials that cannot be used more than once. After removing the dose needed, dispose of all used sterile water vials and needles appropriately. All partially used and empty vials should not be retained, but disposed of in accordance with local requirements. Each vial number and amount used per subject should be carefully documented in the applicable site and pharmacy records.

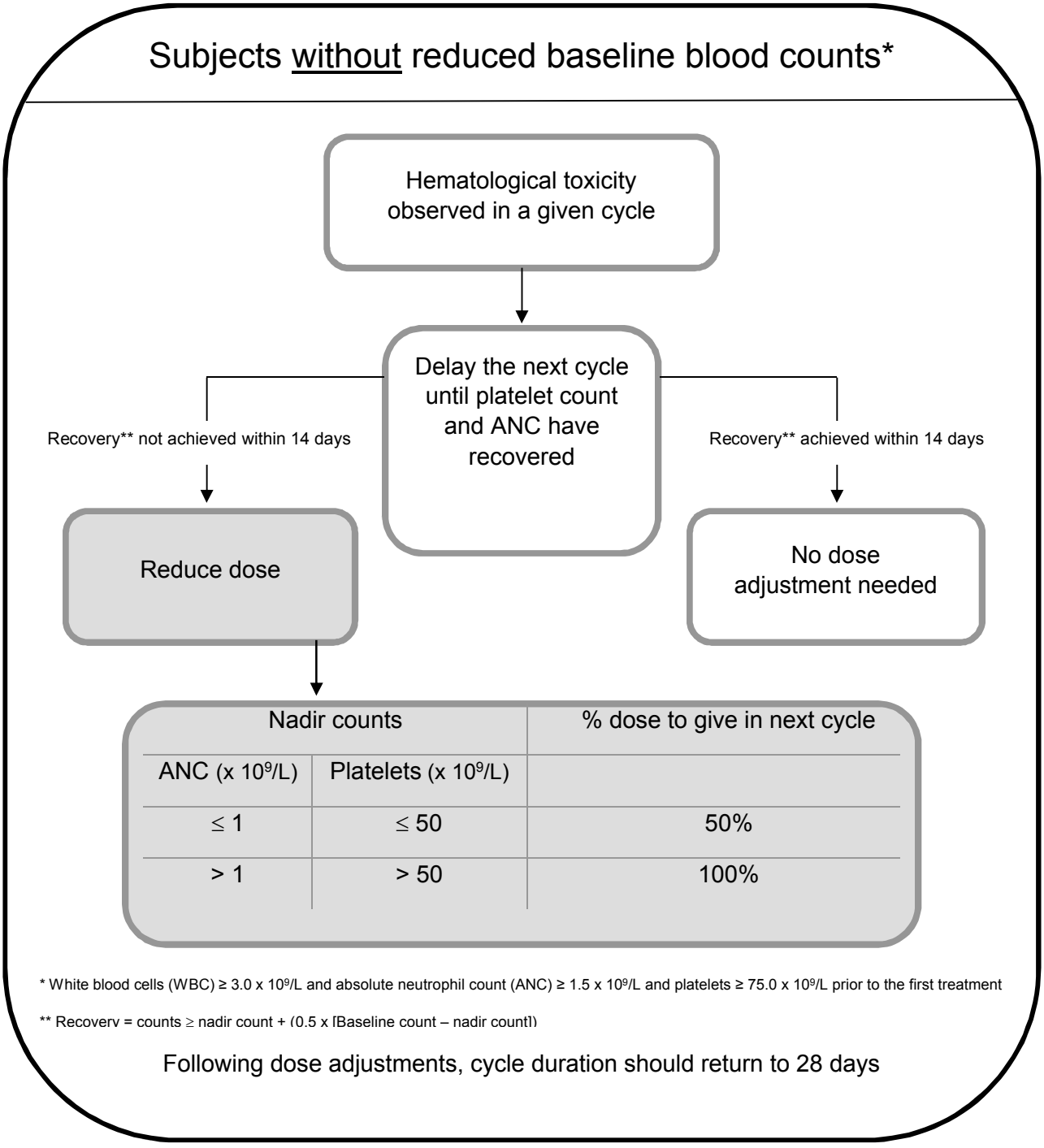
Subcutaneous injection of suspension

1. Select the site(s) for injection: either of the upper arms, thigh, or abdomen. Injection sites within an injection area must be different from 1 injection to the next.
2. Rub the area with a fresh alcohol wipe in an outward circular motion.
3. Remove the plastic cap from the subcutaneous needle, being careful to not touch the needle.
4. Pinch a 2-inch fold of skin at the injection site between your thumb and forefinger.

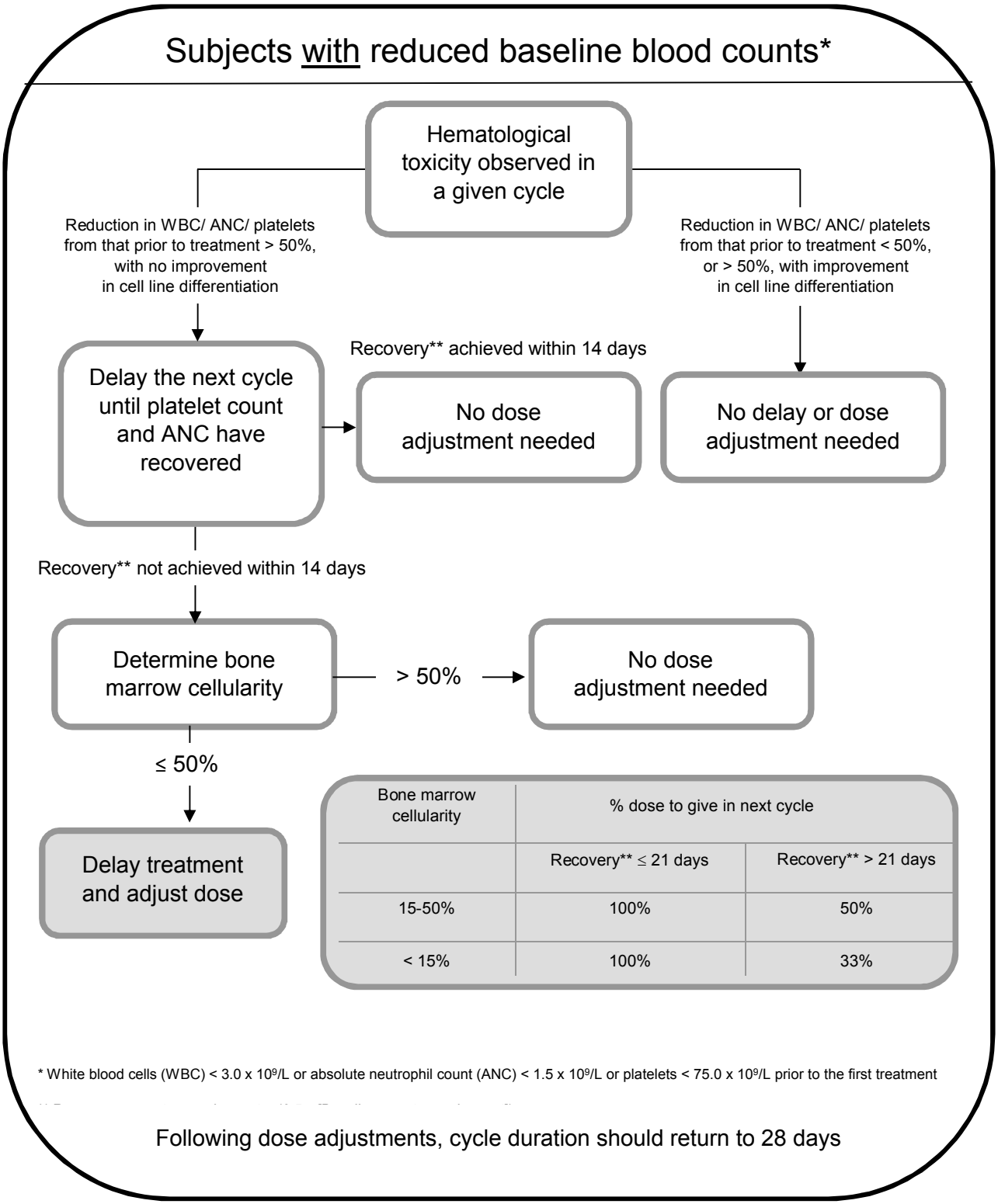
Appendix K: Subcutaneous Preparation and Administration of Azacitidine (Continued)

5. Insert the needle at a 90° angle until it is completely inserted.
6. Pull back on the plunger slightly to check for blood. If blood appears in the syringe, withdraw the syringe and select another site, then repeat steps 2, 4, 5, and 6.
7. If no blood appears in the syringe, push the plunger forward and inject the drug.
8. Withdraw the syringe and swab the area with alcohol.
9. If needed (doses over 100 mg) repeat all the above steps for subcutaneous injection of the suspension. A new location should be selected for administration of each part of the dose. Document location(s) of dose(s) administered.
10. New injections should be given at least 1 inch or 2.5 cm from an old injection site and never into areas where the site is tender, bruised, red, or hard.
11. The details of the dose administration should be recorded in the applicable record(s). When doses exceed 100 mg and/or more than 1 injection is administered, the "time of subcutaneous injection" should be recorded as the time of completion of the last injection.
12. Appropriately dispose of all needles and syringes in accordance with local requirements.

Appendix L: Azacitidine Dose Modifications due to Hematologic Toxicity – Subjects without Reduced Baseline Blood Counts



Appendix M: Azacitidine Dose Modifications due to Hematologic Toxicity – Subjects with Reduced Baseline Blood Counts



Bone marrow cellularity	% dose to give in next cycle	
	Recovery** ≤ 21 days	Recovery** > 21 days
15-50%	100%	50%
< 15%	100%	33%

* White blood cells (WBC) < 3.0 x 10^9/L or absolute neutrophil count (ANC) < 1.5 x 10^9/L or platelets < 75.0 x 10^9/L prior to the first treatment

Appendix N: Cytochrome Sensitive Substrates

From Food and Drug Administration (FDA) Drug Development and Drug Interactions Website: Table 7. Examples [a] of Sensitive In Vivo Cytochrome (CYP) Substrates and CYP Substrates with Narrow Therapeutic Range (7/28/2011)

CYP Enzymes	Sensitive substrates [b]	Substrates with narrow therapeutic range [c]
CYP1A2	Alosetron, caffeine,	Theophylline, tizanidine
	duloxetine, melatonin, ramelteon,	
	tacrine, tizanidine	
CYP2B6 [d]	Bupropion, efavirenz	
CYP2C8	Repaglinide [e]	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A [f]	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil, grapefruit juice	Alfentanil, astemizole [g], cisapride [g], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [g]
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, Venlafaxine	Thioridazine

[a] Note that this is not an exhaustive list. For an updated list, see the following link: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm. Accessed 05 Aug 2015.

[b] *Sensitive CYP substrates* refer to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[c] CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

[d] The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

[e] Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.

[f] Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

[g] Withdrawn from the United States market because of safety reasons.

Appendix O: Transporter Sensitive Substrates

From Food and Drug Administration (FDA) Drug Development and Drug Interactions Website: Table 13. Examples of In Vivo Substrates for Selected Transporters [a] (7/28/2011)		
Transporter	**Gene**	**Substrate**
P-gp	ABCB1	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	ABCG2	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan
OATP1B1	SLCO1B1	Atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38 (active metabolite of irinotecan), rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan
OATP1B3	SLCO1B3	Atorvastatin, rosuvastatin, pitavastatin, telmisartan [b], valsartan, olmesartan
OCT2	SLC22A2	Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin
OAT1	SLC22A6	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	SLC22A8	Acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin, rosuvastatin, sitagliptin

[a] Please note this is not an exhaustive list. For an updated list, see the following link: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm. Accessed 05 Aug 2015.

[b] Selective for OATP1B3.

Appendix P: Monitoring of Liver Function

Subjects with ALT increases of ≥ 3 x ULN will be monitored as follows:

- Liver function tests (ie, ALP, ALT, AST, total bilirubin and GGT) should be repeated within 3 days of the initial ALT finding, 2 to 3 times weekly until ALT level is stable, and weekly thereafter
- Additional diagnostic follow-ups include:
  - Focused medical history, including detailed review of prior history of liver and/or biliary disorders, concurrent symptoms, all concomitant medications (eg, acetaminophen-containing medications, over-the-counter or herbal medications, nutritional supplements) including any changes in medications, and alcohol use
  - Hepatitis serology (anti-HAV antibody, HBsAg, HBcAb, HBsAb, anti-HCV antibody, HCV RNA)
  - Profiling of EBV, CMV and autoantibodies (eg, ANAs, anti-smooth muscle antibodies)
  - Complete physical examination
  - Liver ultrasound and other imaging follow-ups as appropriate
  - Additional evaluations as appropriate (eg, PT with INR and PTT)

Key: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; CMV = Cytomegalovirus ; EBV = Epstein-Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBV = hepatitis B Virus; HBcAb = anti-HBV core antibody; HBsAb = anti-HBV surface antibody; HBsAg = HBV surface antigen; HCV = hepatitis C virus; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; ULN = upper limit of normal.

Celgene Signing Page

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

UserName: [redacted]
Title: [redacted]
Date: Friday, 01 December 2017, 08:46 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- ***Sample size was increased and statistical considerations were updated.***

AG-221 (enasidenib) was approved by the Food and Drug Administration (FDA) in the United States (US) for the treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase 2 (IDH2) mutation as detected by an FDA-approved test. This approval may allow subjects in the conventional care regimen arm to receive commercially available AG-221 (enasidenib), leading to statistical power loss in detecting the treatment effect on overall survival. To remedy this statistical power loss, Study AG-221-AML-004 increased sample size from 280 to 316 subjects and updated statistical considerations (eg, event size was increased from 193 to 250 deaths, etc). (Refer to the Protocol Summary, Section 3.1.1, Figure 1, Section 4.1, and Sections 9.3, 9.6.1, and 9.8.)

- ***Study duration was updated.***

The expected duration of this study was changed from approximately 28 months to 78 months because the enrollment period was extended from 24 months to 42 months to increase the sample size as mentioned above, and to submit the final study report and data set with 3 years of follow-up per the Post Marketing Requirements by the FDA (NDA 209606 APPROVAL 1-Aug-2017 Reference ID: 4132874). Accordingly, the definition of the End of Trial has been updated as either the date of 36 months from the last subject randomized date, or the date when all subjects discontinued from study treatment and no subject is available for survival follow-up, whichever is the later date. (Refer to the Protocol Summary, Table 2, Sections 3.2 and 3.3.)

[redacted]

- ***Fasting (preferred) lipid panel was added at 2 more timepoints.***

Fasting (preferred) lipid panel was added on Day 1 of Cycles 2 and 3 to allow for monitoring lipid changes during early cycles of study treatment. (Refer to Table 3.)

- ***The fasting requirement for lipid panel was updated.***

The most recent European guideline indicates that non-fasting blood samples are sufficient for assessing plasma lipid profiles (Nordestgaard, 2016). Thus, the fasting requirement for lipid panel was updated, particularly for subjects who experience clinically meaningful elevations of lipids, per the investigator's assessment. (Refer to Table 3 and Section 6.2.)

- ***Frequency of assessing disease status in the follow-up phase was reduced.***

The frequency for disease status assessment was reduced from every 8 weeks to every 12 weeks to reduce subjects' burden during follow-up. (Refer to Section 6.3.)

- ***Data collection of investigator-assessed response/ disease status to subsequent AML therapies was added.***

This will allow for evaluate of disease response to subsequent AML therapies after subjects discontinue study treatment. For example, subjects who had refractory disease status before the study treatment might achieve good disease control from subsequent AML therapy after exposure to AG-221. This would provide scientifically meaningful data regarding the sensitivity to subsequent AML therapy after exposure to study treatment, and general disease status after study treatment. (Refer to Table 3 and Section 6.3.)

- ***Fasting requirement for taking AG-221 was removed.***

This change was made based on emerging pharmacokinetics and safety data from a human food effect study (Study AG221-C-002) and two Phase 1/2 dose escalation studies (AG221-C-001 and AG221-C-003) which showed that the increase of AG-221 exposure by food is not considered as clinically meaningful. Accordingly, as recommended by the FDA, the US prescribing information does not include a fasting requirement for AG-221 administration. (Refer to Section 7.2.1.1.)

- ***Reference toxicities during AG-221 therapy were updated.***

These changes were made based on the current AG-221 IB. (Refer to Section 7.2.1.3.)

- ***Restricted concomitant medications during AG-221 therapy were updated.***

Restricted concomitant medications during AG-221 therapy were updated based on the current AG-221 IB. (Refer to Section 8.3.)

The amendment also includes several other minor clarifications and corrections:

- Celgene therapeutic area head signature page was updated on page 3.

[redacted]

- Three new references were cited in Section 9.6.1 (Primary Efficacy Analysis) and have been included in Section 17.

[redacted]

- The commercial test to detect IDH2 mutations has been approved by FDA since August 2017. The explanation was added in Section 6.1.
- Other clarifications, corrections of minor typographical errors and incidental formatting changes were made throughout the document.

2. REFERENCES

Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J. 2016 Jul 1;37(25):1944-58.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- ***Best supportive care was clarified to be given according to local prescribing information and local therapeutic guidelines.***

This clarification was at the request of the French National Agency for Medicines and Health Products Safety (ANSM). (Refer to the Protocol Summary, Sections 3.1.1 and 7.1.5.)

- ***A special condition of allowing confirmation of isocitrate dehydrogenase (IDH) gene mutation locally was added***

In the event that the central laboratory result is delayed and precludes acute clinical management of a subject who has confirmed IDH2 gene mutation by local evaluation, the subject may be eligible for randomization with approval by the Medical Monitor. (Refer to Protocol Summary, Sections 3.1.1 and 4.2 [inclusion criterion #7].)

- ***Management of differentiation syndrome during AG-221 therapy was updated.***

In the upcoming version of the Medical Dictionary for Regulatory Activities (MedDRA), the preferred term of differentiation syndrome associated with therapy of mutant isocitrate dehydrogenase (IDH) inhibition will be IDH Differentiation Syndrome. Thus the term for differentiation syndrome during AG-221 therapy was changed from "Differentiation-like Syndrome" to "IDH Differentiation Syndrome". Diagnosis and treatment of IDH Differentiation Syndrome during AG-221 therapy was also updated with a reference to a supplemental guidance document. (Refer to Protocol Summary, Sections 3.1.1, 7.2.1.3 and 8.)

- ***A note was added to clarify the intermediate-dose cytarabine (IDAC) regimen***

Any local standard regimen different from the IDAC regimen specified in the protocol will need review and approval by the Medical Monitor. (Refer to Protocol Summary, Sections 3.1.1 and 7.2.4.)

- ***For subjects having acute myeloid leukemia (AML) secondary to prior higher risk (Intermediate-2 or High risk according to the International Prognostic Scoring System) myelodysplastic syndromes (MDS) treated with a hypomethylating agent (eg, azacitidine or decitabine), the hypomethylating therapy can be counted as a line/regimen if there is disease progression to AML during or shortly (eg, within 60 days) after the hypomethylating therapy.***

As hypomethylating therapy is approved for higher risk (Intermediate-2 or High risk according to the International Prognostic Scoring System) MDS and AML (approvals vary by country), and secondary AML with prior MDS treated with hypomethylating therapy has the median overall survival only about 4 months, as poor as those who have failed second- or third-line AML therapy, this amendment will count the hypomethylating therapy for higher risk MDS as a line/regimen if there is disease progression to AML during or shortly (eg, within 60 days) after the hypomethylating therapy. (Refer to Sections [redacted] 4.2 [inclusion criterion #9] and 17, and Appendix G.)

[redacted]

[redacted]

- ***Caution of AG-221 phototoxicity was removed.***

AG-221 does not possess phototoxicity potential based on its exposure to BALB/c-3T3 mouse fibroblasts in the presence of ultraviolet (UV) radiation. Thus caution of AG-221 phototoxicity was removed. (Refer to Sections [redacted] 7.2.1.3.)

- ***A new response criterion, morphologic complete remission with partial hematologic recovery (CRh) was added.***

The new response criterion, CRh is defined as all criteria of morphologic CR except that absolute neutrophil count (ANC) > 0.5 x 10^9/L (500/μL) and platelet count > 50 x 10^9/L (50,000/μL). This criterion will be assessed by the Sponsor only and based on laboratory dataset. (Refer to Table 2, Section 9.6.2.2, and Appendix F.)

- ***The formula for creatinine clearance calculation was updated***

The Cockcroft-Gault formula was replaced by the Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR). (Refer to Section 4.2 [inclusion criteria #8])

- ***The requirement for cytarabine pregnancy prevention was updated for female subjects and male subjects with their partners.***

These updates were made at the request of health authorities in reference to the contraceptive recommendations in the summary of product characteristics (SmPC) of cytarabine (ie, effective contraception during treatment and up to 6 months after stopping it). (Refer to Sections 3.1.3, 4.2 [inclusion criteria #9 and #10], 6.3, and 10.4.)

- ***The requirement for the minimum number of treatment cycles was clarified for subjects refractory to, or relapsed after, second- or third-line/regimen of intensive therapy for AML.***

This clarification was made at the request of the ANSM. Intensive therapy as the second- or third-line/regimen for AML subjects 60 years or older (as required by the study) would need extensive customization which could be best achieved through the treating physician's assessment. Thus, the protocol does not specify the minimum number of treatment cycles required to define refractory or relapsed disease after intensive therapy as the second- or third-line/regimen for AML. (Refer to Section 4.2 [inclusion criterion #4a].)

- ***The eligibility of subjects to the conventional care regimen (CCR) treatment option was further clarified that subjects with degenerative and toxic encephalopathy should not receive cytarabine.***

This addition was made at the request of the ANSM in reference to the section of Contraindications in the SmPC of cytarabine. (Refer to Section 4.2 [inclusion criterion #5].)

- ***The definition of females of childbearing potential (FCBPs) was updated.***

This update was made in reference to "Recommendations related to contraception and pregnancy testing in clinical trials" by Clinical Trial Facilitation Group (CTFG). (Refer to Section 4.2 [inclusion criterion #9].)

- ***Effective contraceptive methods were clarified.***

This clarification was made in reference to "Recommendations related to contraception and pregnancy testing in clinical trials" by CTFG. (Section 4.2 [inclusion criteria #9 and #10].)

- ***True abstinence was incorporated into the requirement for pregnancy prevention.***

This update was made at the request of Medicines and Healthcare products Regulatory Agency (MHRA). (Refer to Section 4.2 [inclusion criteria #9 and #10])

- ***Management of leukocytosis with hydroxyurea was updated.***

The threshold of white blood cell (WBC) count was removed to allow control of leukocytosis with hydroxyurea per standard institutional practice. (Refer to Sections 4.2 [exclusion criterion #4], 7.2.1.3 and 8.)

- ***Exclusion of subjects taking specific medications known to prolong QT interval was clarified***

Subjects taking specific medications that are known to prolong QT interval will be excluded unless the subjects can be transferred to other medications at least 5 half-lives prior to the start of study treatment. (Refer to Section 4.3 [exclusion #18].)

- ***A guideline for monitoring liver function was added***

The guideline was added as an example of acute clinical management. (Refer to Section 6.4.2 and Appendix P.)

- ***Management of gastrointestinal disorders during AG-221 therapy was added.***

This addition was made at the request of the ANSM in reference to the current AG-221 IB and in line with the IB. (Refer to Section 7.2.1.3.)

- ***A recommendation of the minimum number of AG-221 treatment cycles was added.***

Preliminary data from the Phase 1/2 study (ie, AG-221-C-001) showed that response to treatment with AG-221 may frequently be delayed. Thus it is recommended that subjects receive at least 6 cycles of AG-221 treatment in order to optimally benefit from the treatment. (Refer to Section 7.2.1.)

- ***Definitions of hematologic toxicities were clarified.***

These clarifications were made to allow continuous AG-221 treatment cycles without delays due to disease-related hematologic toxicities. (Refer to Section 7.2.1.3.)

- ***Criteria for initiating subsequent AG-221 treatment cycle was updated.***

This update was made to allow continuous AG-221 treatment cycles without delays due to disease-related adverse events. (Refer to Section 7.2.1.4.)

- ***The definition of subjects without reduced baseline blood counts was updated.***

These updates were made at the request of the ANSM in reference to the current Azacitidine IB and in line with the IB. (Refer to Section 7.2.2.1 and Appendix L.)

- ***Management of necrotizing fasciitis during azacitidine therapy was added.***

This addition was made at the request of the ANSM in reference to the azacitidine SmPC. (Refer to Section 7.2.2.1.)

- ***Guidelines of concomitant treatment of gastrointestinal side effects during azacitidine treatment were added.***

Recommended concomitant treatment of nausea, vomiting and/or diarrhea during azacitidine treatment was added. (Refer to Section 8.1.)

- ***Administration of live or live-attenuated vaccines was added as a prohibited concomitant medication during the course of cytarabine therapy.***

This addition was made at the request of the ANSM in reference to the section "Special warnings and precautions for use" in the cutarabine SmPC. (Refer to Section 8.2.)

- ***Administration of 5-Fluorocytosine was added as a prohibited concomitant medication during the course of cytarabine therapy.***

This addition was made at the request of the ANSM in reference to the section of Interaction with medicinal products and forms of interaction in the cytarabine SmPC. (Refer to Section 8.2.)

The amendment also includes several other minor clarifications and corrections:

- Medical monitor contact information and Celgene therapeutic head signature page were updated on pages 2 and 3.

[redacted]

- Citations of AG-221 and azacitidine IBs were removed in Section 17 and the links to these citations (in the Protocol Summary, and Sections [redacted] 10.6) were abolished to allow reference to the current IBs.

[redacted]

- Multi-gated acquisition (MUGA) scan was removed as an assessment during screening and/or treatment. However, a prior MUGA scan performed within 28 days prior to the start of study treatment can be used for study entry. These changes were reflected in the Protocol Summary, Table 3, and Sections 6.1, 6.2, and 6.4.
- The window for bone marrow aspirate and/or biopsy, peripheral blood smear and, if applicable, cytogenetics, during the Treatment Phase was clarified in the footnotes "w", "x" and "y" of Table 3 to be consistent with Section 6.2.
- The window for bone marrow aspirate and/or biopsy, peripheral blood smear and, if applicable, cytogenetics, during the Follow-up Phase was corrected in Section 6.3 to ± 14 days to be consistent with the footnote "q" of the Protocol, Table 3, Table of Events.
- The parameters of chemistry and cardiac marker panels were updated.
- Truncated sentences in Sections 8.1 and 10.6 were completed.
- The elapsed time from azacitidine reconstitution to administration in Method A of Appendix K was updated with addition of the specification in the United States.
- Specification of azacitidine reconstitution with refrigerated water was added in Method B of Appendix K.
- Corrections of minor typographical errors and incidental formatting changes were made throughout the document.