Official Title of Study:

A Phase 1b/2 Open-Label, Randomized Study of 2 Combinations of Isocitrate Dehydrogenase (IDH) Mutant Targeted Therapies Plus Azacitidine: Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus SC Azacitidine in Subjects With Newly Diagnosed Acute Myeloid Leukemia Harboring an IDH1 or an IDH2 Mutation, Respectively, Who Are Not Candidates to Receive Intensive Induction Chemotherapy

PROTOCOL(S) AG-221-AML-005

NCT Number: NCT02677922

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A PHASE 1B/2 OPEN-LABEL, RANDOMIZED STUDY OF 2 COMBINATIONS OF ISOCITRATE DEHYDROGENASE (IDH) MUTANT TARGETED THERAPIES PLUS AZACITIDINE: ORAL AG-120 PLUS SUBCUTANEOUS AZACITIDINE AND ORAL AG-221 PLUS SC AZACITIDINE IN SUBJECTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA HARBORING AN IDH1 OR AN IDH2 MUTATION, RESPECTIVELY, WHO ARE NOT CANDIDATES TO RECEIVE INTENSIVE INDUCTION CHEMOTHERAPY

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SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information
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Title: [redacted]
Address: [redacted]
Phone: [redacted]
E-mail: [redacted]

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

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

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for 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 1b/2 Open-Label, Randomized Study of 2 Combinations of Isocitrate Dehydrogenase (IDH) Mutant Targeted Therapies Plus Azacitidine: Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus SC Azacitidine in Subjects With Newly Diagnosed Acute Myeloid Leukemia Harboring an IDH1 or an IDH2 Mutation, Respectively, Who Are Not Candidates to Receive Intensive Induction Chemotherapy

Indication

Treatment of patients 18 years and older with newly diagnosed acute myeloid leukemia (AML) with an IDH1 or an IDH2 mutation who are not candidates to receive intensive induction chemotherapy (IC).

Key Objectives

Phase 1b Dose-finding Stage

Primary Objectives

- To assess the safety and tolerability of the combination treatments of oral AG-120 when administered with subcutaneous (SC) azacitidine and oral AG-221 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive IC.
- To establish the recommended combination dose (RCD) of oral AG-120 and oral AG-221 when administered with SC azacitidine.

Secondary Objective

- To assess the preliminary efficacy of the combination treatments of oral AG-120 when administered with SC azacitidine and oral AG-221 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive IC.

Phase 1b AG-120 Expansion Stage

Primary Objectives

- To assess the safety and tolerability of the combination treatments of oral AG-120 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 mutation who are not candidates to receive intensive IC.

Secondary Objective

- To assess the preliminary efficacy of the combination treatments of oral AG-120 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 mutation, who are not candidates to receive intensive IC.
- To characterize the pharmacokinetics (PK) of oral AG-120 when administered with SC azacitidine.

Phase 2 AG-221 Randomized Stage

Primary Objective

- To assess the efficacy of oral AG-221 when administered with SC azacitidine versus SC azacitidine alone in subjects with newly diagnosed AML with an IDH2 mutation, who are not candidates to receive intensive IC.

Secondary Objectives

- To evaluate the safety of oral AG-221 when administered with SC azacitidine.
- To characterize the PK of oral AG-221 when administered with SC azacitidine.
- To evaluate the effect of oral AG-221 when administered with SC azacitidine versus SC azacitidine alone on health-related quality-of-life (HRQoL) outcomes.

[redacted]

Study Design

This Phase 1b/2 study is an open-label, randomized, multicenter trial to evaluate the safety and efficacy of oral AG-120 + SC azacitidine and oral AG-221 + SC azacitidine in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively. The study population consists of subjects who are not candidates to receive intensive IC. The study comprises a Phase 1b dose-finding and AG-120 expansion stage and a Phase 2 randomized stage [redacted].

Phase 1b Dose-finding Stage

The Phase 1b stage is an open-label dose-finding study to evaluate the safety and tolerability of oral AG-120 and oral AG-221 administered with SC azacitidine to define the RCD of these 2 agents when administered with SC azacitidine. The preliminary clinical activities of the oral AG-120 + SC azacitidine and the oral AG-221 + SC azacitidine regimens will also be assessed.

The Phase 1b stage consists of 3 periods: 1) screening; 2) treatment; and 3) follow-up.

Subject screening procedures will occur during the screening period within 28 days prior to the start of study treatment. The diagnosis of AML with an IDH mutation will be based on local review of both hematopathology and IDH gene mutation testing of bone marrow aspirate and/or peripheral blood samples. Subjects eligible for enrollment must not be candidates to receive intensive IC, based on the investigator's judgment, due to the presence of co-morbidities, declining performance status, or other factors. Subjects with newly diagnosed AML with an IDH1 mutation will be assigned to the oral AG-120 + SC azacitidine arm, and subjects with newly diagnosed AML with an IDH2 mutation will be assigned to the oral AG-221 + SC azacitidine arm. In the rare case in which a subject is diagnosed with an AML associated with dual IDH1 and IDH2 mutations, assignment to the oral AG-120 or AG-221 treatment arm will be based on a joint investigator and medical monitor decision and documented in the source.

During the treatment period a standard 3 + 3 design will be used (Section 3.1.1). A Dose Review Team (DRT), consisting of a Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives or designees, as appropriate, and all active site investigators and/or designees (at sites with a subject who has received study drug), will review all adverse events (AEs) experienced by subjects during Cycle 1 of each dose level to determine whether the maximum tolerated dose (MTD) of oral AG-120 or AG-221 when administered with SC azacitidine has been exceeded. One dose level of oral AG-120 (500 mg daily) and 2 dose levels of oral AG-221 (100 mg daily and 200 mg daily) are planned to be evaluated. Dose levels lower than 500 mg daily for oral AG-120 and lower than 100 mg daily for oral AG-221 will be evaluated if these doses when administered with SC azacitidine are found to exceed the MTD during Cycle 1. Dose interruptions/delays and dose reductions may be used to manage toxicities. Subjects may receive study treatment until disease progression/relapse, study treatment becomes intolerable, or the subject wishes to discontinue study treatment for any reason. Response to treatment will be assessed by the investigators according to the modified International Working Group (IWG) AML Response Criteria (Cheson, 2003) (Appendix F). Hematologic improvement (HI) in subjects with newly diagnosed AML will also be assessed according to the IWG myelodysplastic syndromes HI criteria (Cheson, 2006) (Appendix G). Subjects are to undergo end-of-treatment evaluations when study treatment is discontinued (Section 3.1.2.3). The reason for treatment 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 AEs, concomitant medications, concomitant procedures, transfusions, [redacted] response, hematologic improvement, subsequent AML therapies, and survival.

- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up or disease progression will continue to be assessed during the Follow-up period of the study for response until disease progression (Section 6.3).
- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up will continue to be assessed for subsequent AML therapies, and survival (Section 6.3).

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

Phase 1b AG-120 Expansion Stage

A Phase 1b expansion cohort of approximately 15 subjects with newly diagnosed AML with IDH1 mutation will be enrolled to the AG-120 combination (Section 3.1.1.4). Subjects enrolled in the AG-120 expansion will receive the AG-120 + azacitidine at the RCD.

Phase 2 AG-221 Randomized Stage

The Phase 2 stage is an open-label randomized study to evaluate the efficacy of oral AG-221 with SC azacitidine versus SC azacitidine alone in order to assess the overall response rate (ORR) and event-free survival (EFS).

The Phase 2 stage will also consist of 3 periods: 1) screening; 2) treatment; and 3) follow-up.

As with Phase 1b, subject screening procedures will occur during the screening period within 28 days prior to the start of study treatment, but the diagnosis of AML will be performed locally for enrollment and retrospectively confirmed based on a subsequent central pathology review. IDH mutational status will be assessed locally, and for sites without local testing capabilities a referral lab will be identified. A bone marrow aspirate and peripheral blood sample must be sent [redacted] to the central lab for potential retrospective confirmation of mutational status. Inclusion in the trial can be based on local IDH testing. Subjects eligible for enrollment are those who are not candidates to receive intensive IC, based on the investigator's judgment, due to the presence of co-morbidities, declining performance status, or other factors.

Following review of eligibility, subjects with newly diagnosed AML with an IDH2 mutation will be randomized to receive oral AG-221 + SC azacitidine (Arm 1) versus SC azacitidine alone (Arm 2) in a 2:1 ratio. Arm 1 will include a minimum of 66 subjects and Arm 2 will include a minimum of 33 subjects, (99 subjects total in both arms).

Subjects will be stratified by primary (ie, de novo) or secondary (progression of myelodysplastic syndrome (MDS) or myeloproliferative neoplasms [MPN], or therapy-related) AML according to the WHO classification (Appendix B).

Study treatment will start within 3 days of randomization. Assessments during study treatment include efficacy, safety, HRQoL, [redacted] pharmacokinetics, pharmacodynamics, [redacted].

During both Phase 1b and Phase 2 a retrospective central pathology review of all bone marrow aspirates and/or biopsies and peripheral blood smears collected during screening will be conducted by personnel blinded to subject treatment to confirm eligibility. Bone marrow aspirate (BMA) and/or biopsy and peripheral blood smear collected after the start of study treatment must be available for both local and central pathology review. The retrospective central pathology review, will require a set of duplicate slides for each bone marrow collection time point including BMA, peripheral blood smear, and bone marrow biopsy (BMB) if performed. The central pathology review will be conducted by personnel blinded to study treatment.

Response to treatment and HI will be assessed by the investigators according to modified IWG AML Response Criteria (Cheson, 2003) (Appendix F) and IWG myelodysplastic syndromes HI criteria (Cheson, 2006) (Appendix G), respectively.

Dosing interruptions, dosing delays or dose modifications may occur for managing toxicities and/or augmenting treatment response during study treatment (Section 7.2.2.3.1) and (Section 7.2.2.3.4).

The discontinuation of AG-120, AG-221, or azacitidine for subjects in the combination arms of the study is allowed. Subjects may continue treatment with single agent AG-120, AG-221, or azacitidine if in the investigator's assessment the subject continues to show clinical benefit and all protocol-specified criteria for continuing study treatment are met. Study treatment will be discontinued if the subject has progressive disease (Appendix F) or receives alternative therapies. 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, it

is recommended that the investigator 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 AEs, concomitant medications, concomitant procedures, transfusions, [redacted] response, hematologic improvement, subsequent AML therapies, and survival.

- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up or disease progression will continue to be assessed during the Follow-up period of the study for response until disease progression (Section 6.3).
- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up will continue to be assessed for subsequent AML therapies, and survival (Section 6.3).

Length of Study

The full length of the study is expected to be approximately 96 months including recruitment, screening, treatment, and follow up for Phase 1b, Phase 2 [redacted]. For a single subject, the expected duration of the study is approximately 30 months, including a screening period for up to 28 days, inclusive of overall survival.

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

Study Treatments

AG-120 and AG-221 are administered orally once a day (QD) on Days 1-28 of each 28-day cycle. Subjects should be instructed to take their daily dose at approximately the same time each day ± 6 hours. 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. Fasting is required for 2 hours prior to and 1 hour following AG-221 administration. Water is allowed during fasting. Fasting is not required for AG-120 administration.

Azacitidine will be administered SC for 7 days of each 28-day treatment cycle starting on Day 1 during both Phase 1b and Phase 2. Subjects with newly diagnosed AML who are currently receiving their 1st cycle of azacitidine can be screened for the study. On study, Cycle 1 must be started at 28 days after initiation of the pre-study azacitidine.

During the Phase 2 stage, subjects randomized to the azacitidine alone arms will receive azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle. All randomized subjects will receive azacitidine 75 mg/m^2/day SC for 7 days every 28 days until the end of the study, unless they are discontinued from the treatment. In addition, subjects may receive best supportive care as needed (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 best supportive care; (see current version of Prescribing Information), including antibiotics and transfusions, per investigator discretion. In the event that 2 or fewer doses are missed during the 7-day dosing period, dosing should continue so the subject receives the full 7 days of therapy. If 3 or more days are missed during the 7-day dosing period, the investigator should contact the sponsor and a decision on dosing will be made on a case-by-case basis.

Phase 1b (Dose-finding and AG-120 Expansion) Stage:

Phase 1b dose finding will use a 3 + 3 design. For AG-120 one dose level will be explored enrolling a minimum of 3 subjects. Cohort 1 will be initiated with oral AG-120 500 mg once a day and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle. A Cohort -1 will be explored with AG-120 250 mg once a day and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle if 2 or more subjects in Cohort 1 have a dose-limiting toxicity (DLT) in cycle 1. Upon declaration of the RCD by the DRT an expansion cohort of up to 15 patients will be enrolled at the RCD for further safety evaluation and PK sampling.

For AG-221 two dose levels will be explored. Cohort 1 will be initiated with oral AG-221 100 mg once a day and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle. If no DLTs are observed, the RCD will be confirmed by the DRT and the 100 mg dose will be used as the starting dose for Phase 2 of the study. Dose escalation to Cohort 2 will be initiated with oral AG-221 200 mg once a day and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle to explore the tolerability of AG-221 + SC azacitidine at this dose level. A Cohort -1 with oral AG-221 50 mg daily and azacitidine

75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle will be explored if 2 or more subjects have a DLT in Cohort 1.

The DRT will evaluate all toxicities of each subject after 1 cycle and determine whether further dose modifications are needed for individual subjects (Section 3.1.1.2).

Phase 2 AG-221 Randomized Stage:

AG-221 + Azacitidine Arm (Arm 1):

- Subjects with an IDH2 mutation will receive AG-221 at the RCD orally QD on Days 1-28 of each 28-day cycle + azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle.

Azacitidine Arm (Arm 2):

- Subjects with IDH2 mutation will receive azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle.

[redacted]

Overview of Key Efficacy Assessments

Efficacy

Serial blood and bone marrow sampling will be used to determine response to therapy starting at Cycle 2. Both response and hematologic improvement (HI) will be assessed locally by the investigators using modified IWG AML response criteria (Cheson, 2003) and IWG response criteria in myelodysplasia (Cheson, 2006), and retrospectively by a blinded Independent Response Adjudication Committee (IRAC) if the study data will be used for regulatory activities. [redacted] The site needs to ensure peripheral blood for central hematology is collected and sent at the time of every bone marrow collection.

A retrospective pathology review will be performed. The retrospective central pathology review, will require a set of duplicate slides for each bone marrow collection time point including BMA, peripheral blood smear, and BMB if performed. The central pathology review will be conducted by personnel blinded to study treatment.

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

Subjects who discontinue study treatment prior to relapse or progression will complete monthly site visits until confirmation of relapse or progression. For subjects who have discontinued study treatment due to relapse or progression, monthly follow up can be performed by site visits or phone calls. Subjects will be followed until they have died, are lost to follow up, withdraw consent for further data collection, or until study closure.

Overview of Other Key Assessments

Safety

Safety assessments include adverse events, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan, electrocardiogram (ECG), cardiac markers, urinalysis, coagulation, hematology, serum chemistry, transfusions, pregnancy testing (for females of child bearing potential (FCBP) only), and concomitant medications or procedures.

Plasma PK/PD of AG-120 and AG-221

The PK profile of AG-120 when administered with SC azacitidine will be evaluated by plasma concentrations and PK parameters of AG-120 in the Phase 1b expansion segment. Plasma concentrations of 2-HG will be evaluated in relation to plasma concentrations of AG-120 over time.

The PK profile of AG-221 when administered with SC azacitidine will be evaluated by plasma concentrations and PK parameters of AG-221 in the Phase 2 segment. Plasma concentrations of 2-HG will be evaluated in relation to plasma concentrations of AG-221 over time.

[redacted]

Investigational product accountability

Oral AG-120 and AG-221 are dispensed on Day 1 of each treatment cycle and accounted for after completion of each treatment cycle.

Azacitidine will be administered SC by study site personnel. Accurate recording of all IP dosing, will be made in the appropriate section of the subject's eCRF and source documents.

[redacted]

Statistical Methods

Phase 1b (Dose-finding and AG-120 Expansion) Stage:

Statistical analyses in Phase 1b will be primarily descriptive in nature. Tabulations will be produced for disposition, demographic and baseline disease characteristics, safety, PK, PD, and clinical activity parameters. Categorical data will be summarized by frequency distributions (numbers and percentages of subjects) and continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Data will be summarized by dose level and overall when appropriate.

Phase 2 AG-221 Randomized Stage:

The primary efficacy endpoint of Overall Response Rate (ORR) in Phase 2 includes responses of CR, CRp, CRi, morphologic leukemia-free state (MLFS), and PR, according to modified IWG AML response criteria. The treatment difference in ORR will be tested using the Chi square test in the ITT population. This test will provide the pivotal p-value for the comparison of the ORRs of oral AG-221 + SC azacitidine versus azacitidine mono therapy group.

Approximately 99 subjects will be randomized in this study with 66 IDH2 subjects in the oral AG-221 + SC azacitidine arm, and 33 IDH2 subjects in the SC azacitidine mono therapy arm. Assuming an ORR of 30% in the azacitidine mono therapy arm and an ORR of 50% for oral AG-221 + SC azacitidine arm this designed sample size (66 in the AG-221 + SC azacitidine and 33 in the azacitidine mono therapy arm) will provide 75% power to detect an 20% difference in ORR at a Type I error rate of 0.2 (two-sided).

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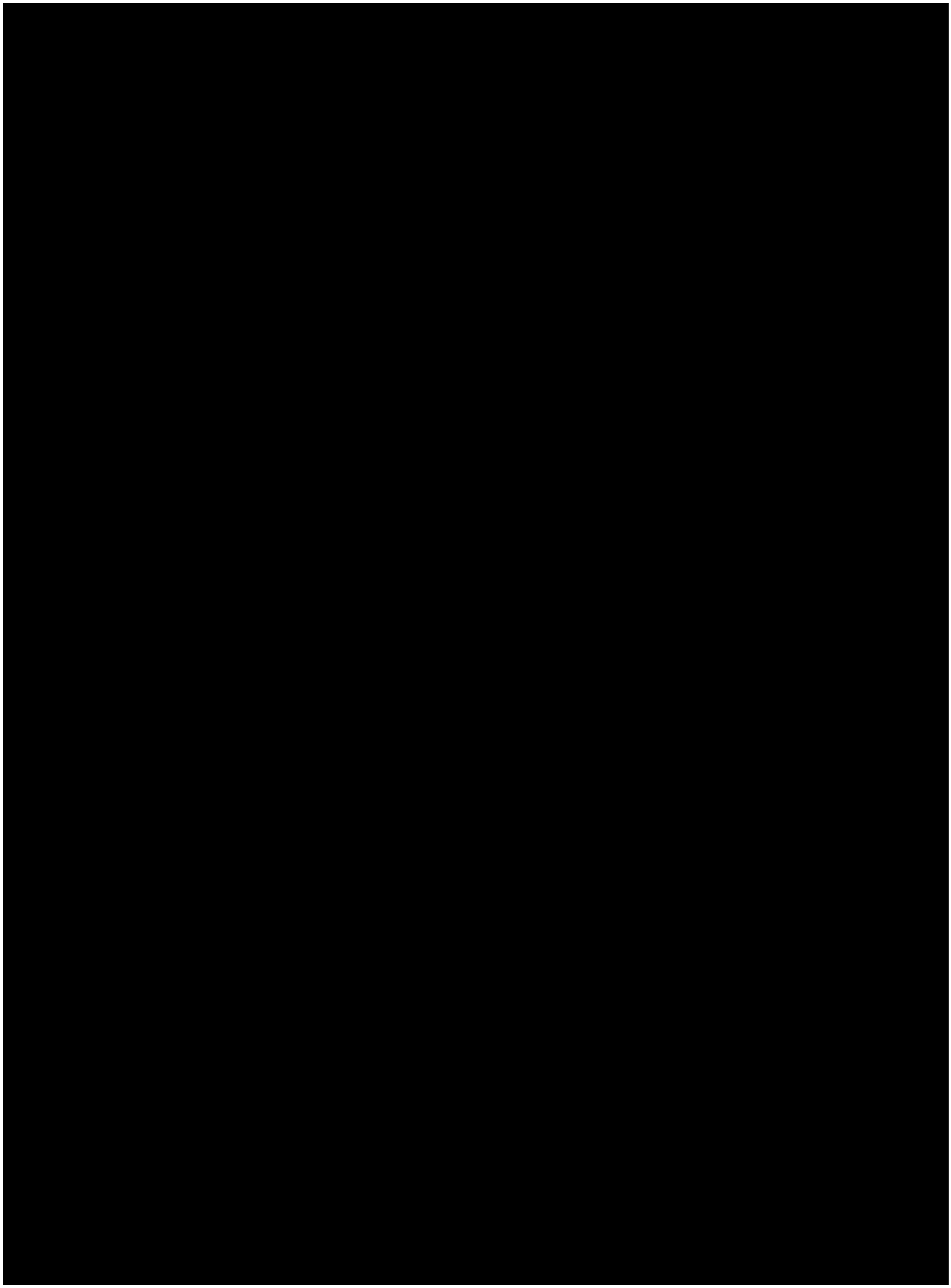
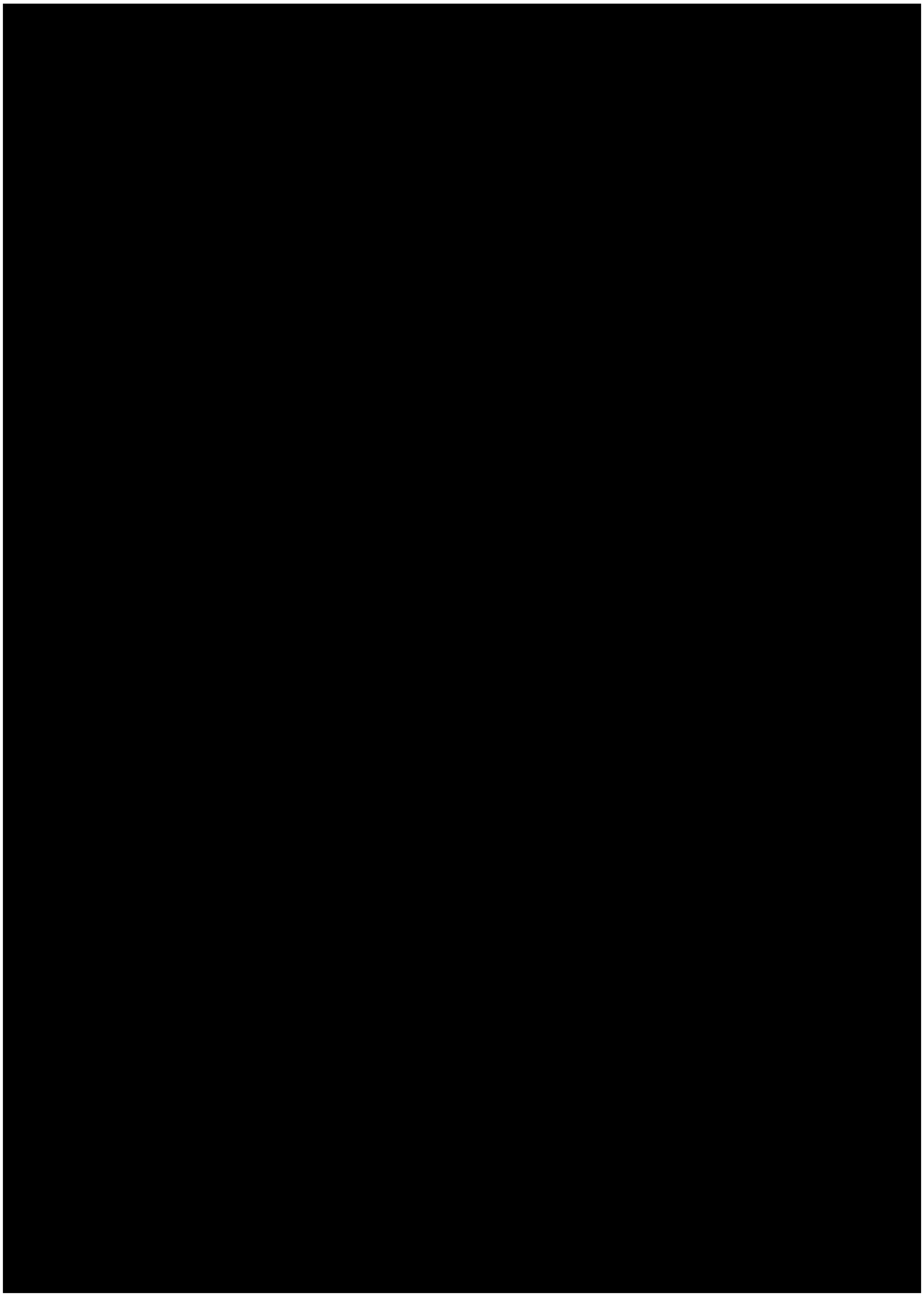
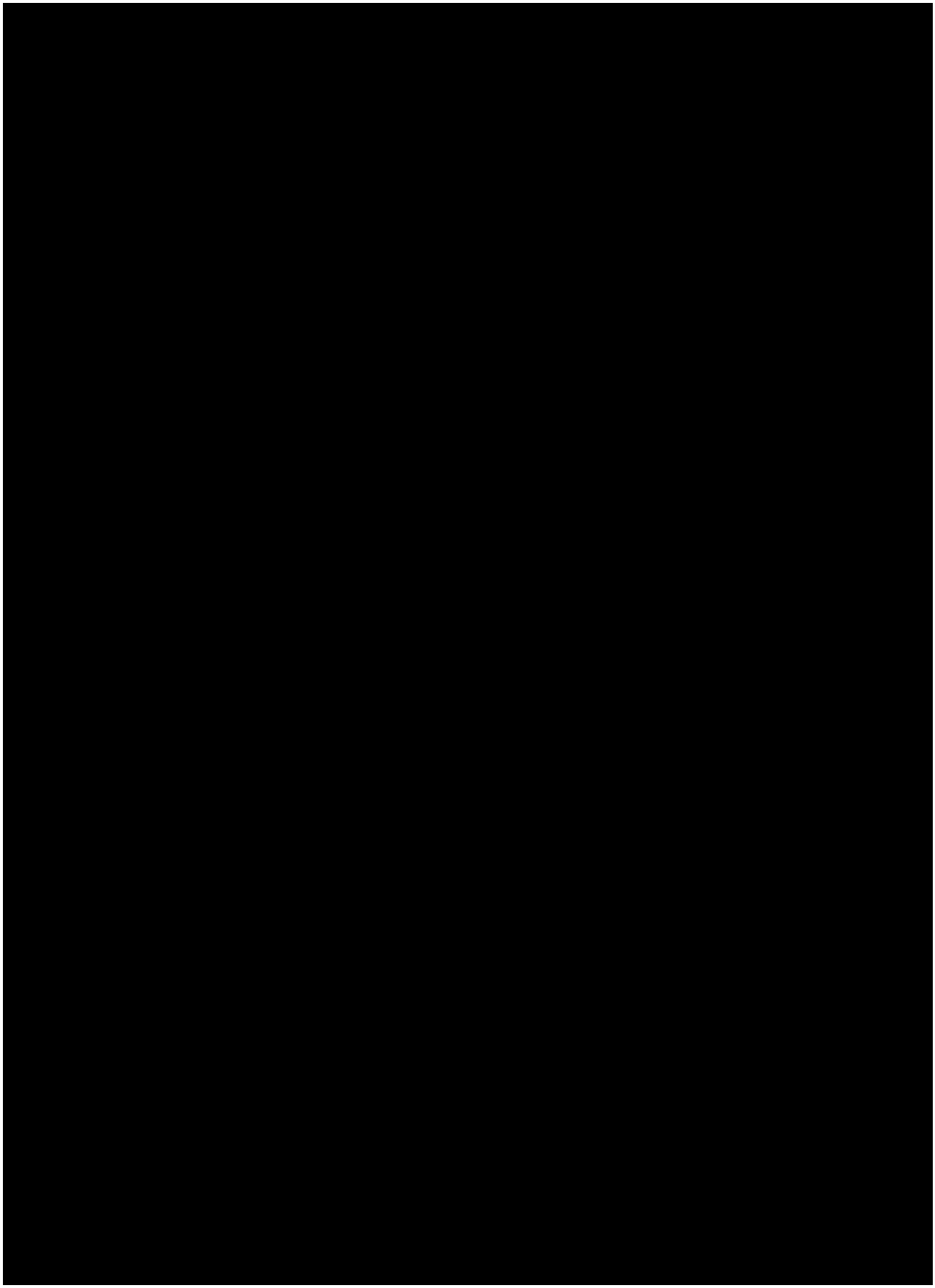
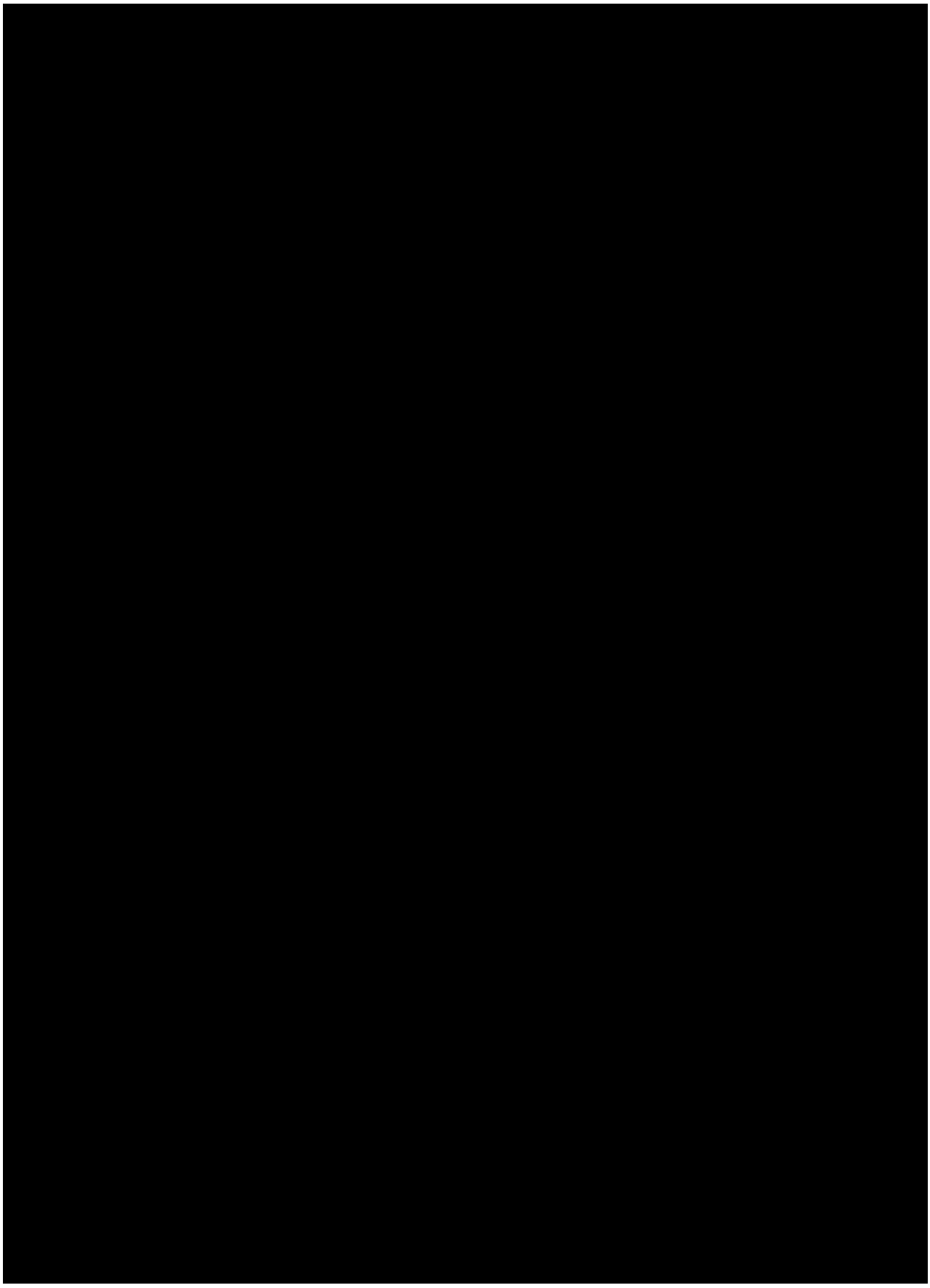
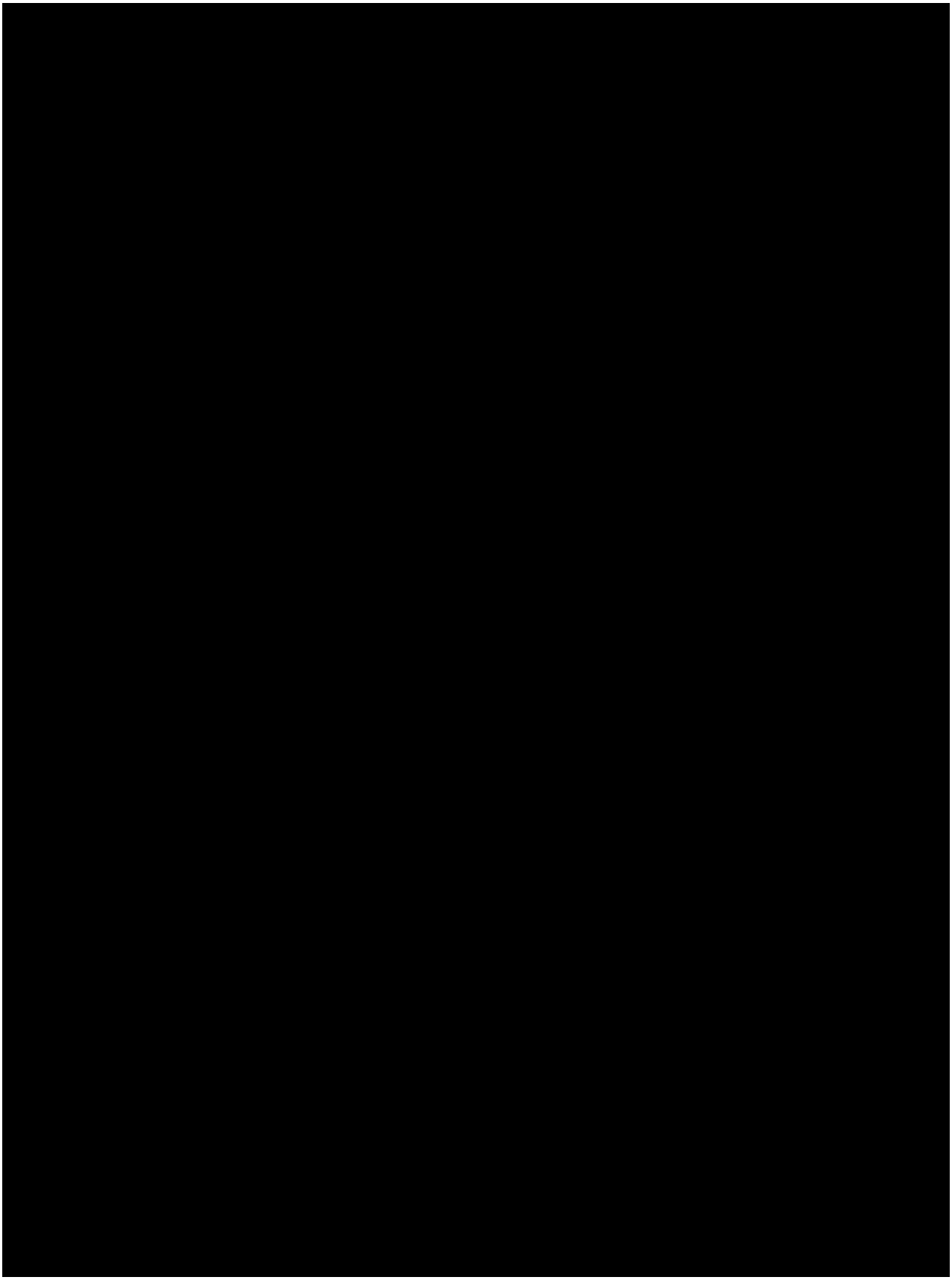
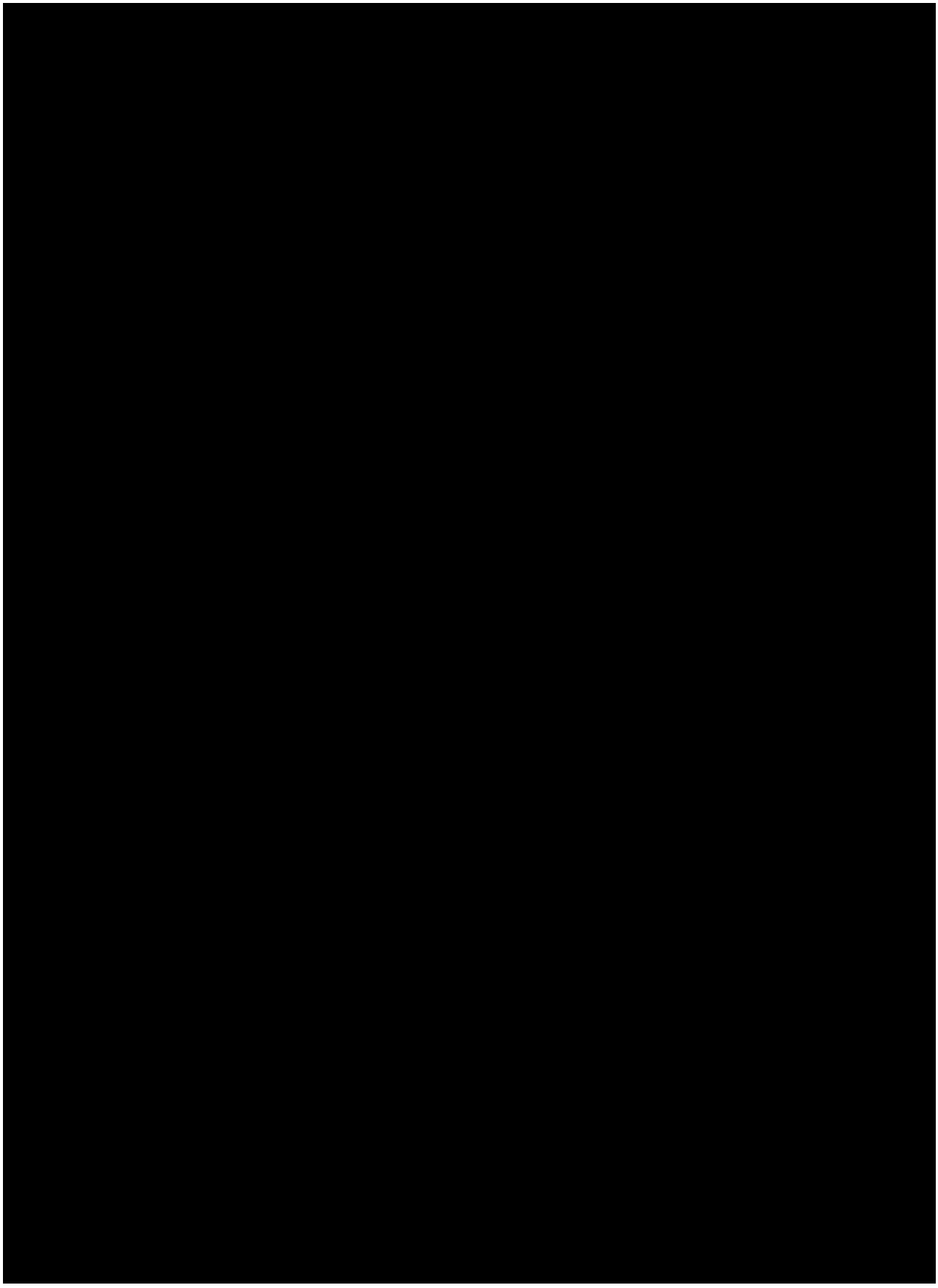


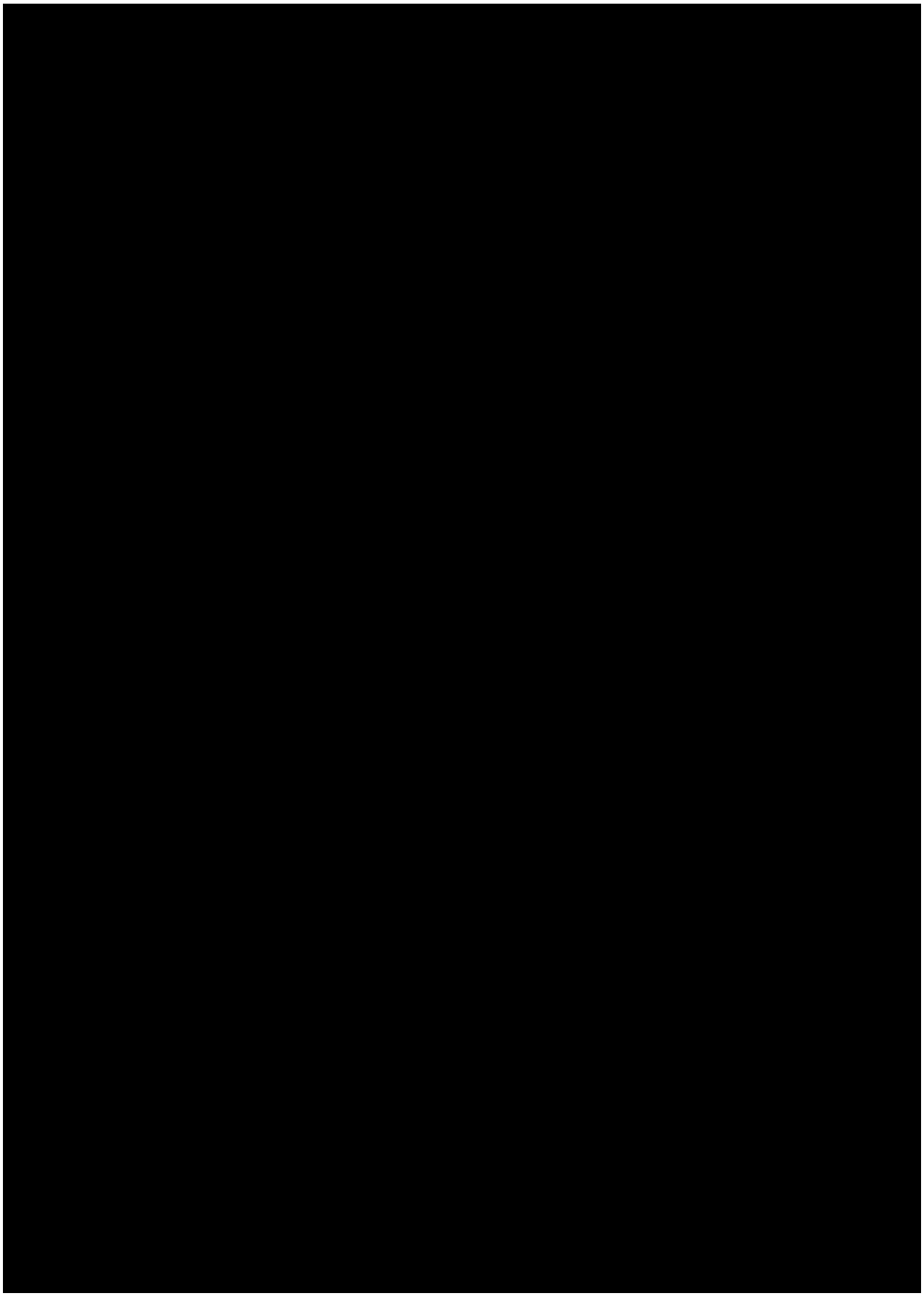


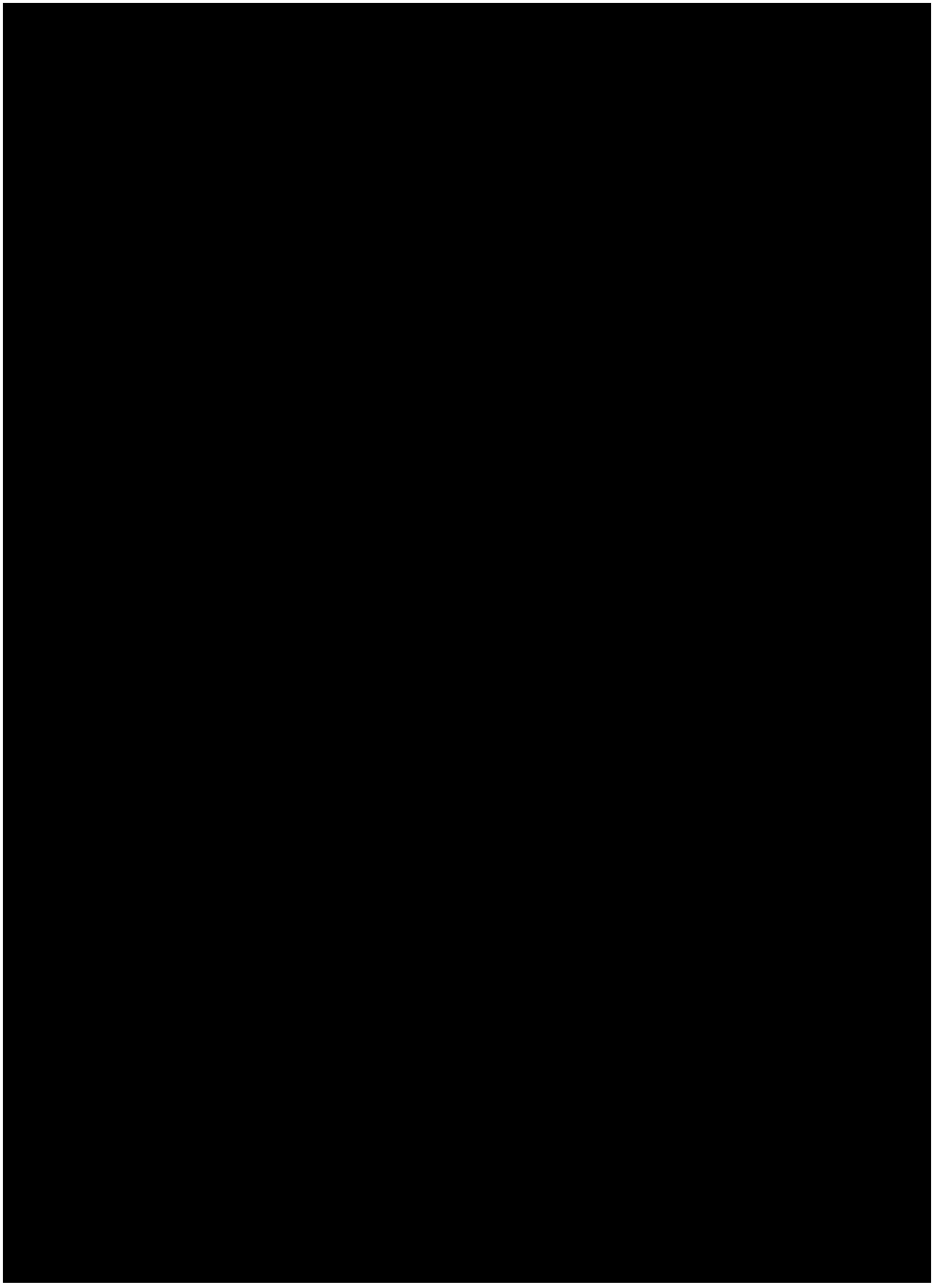


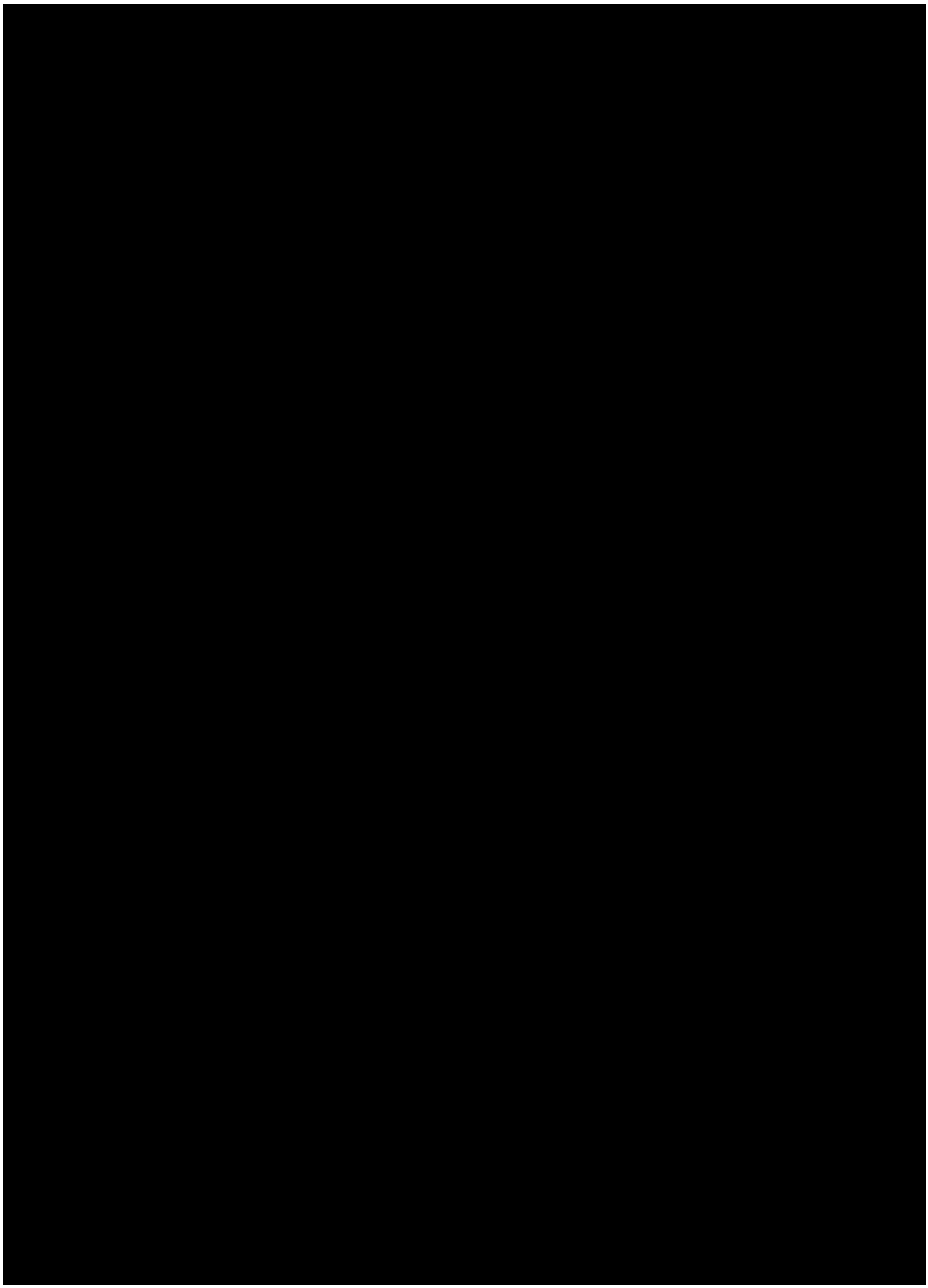


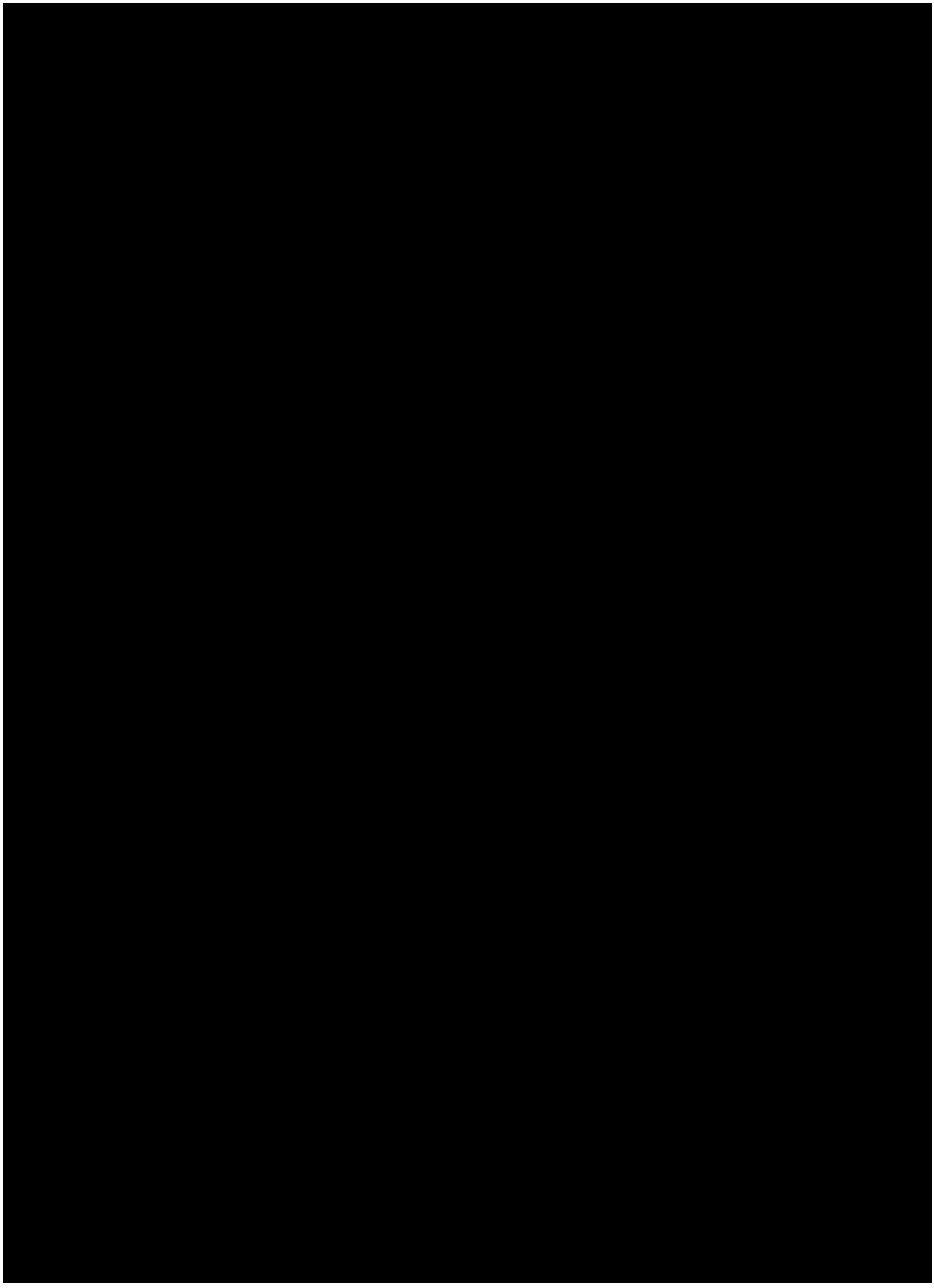


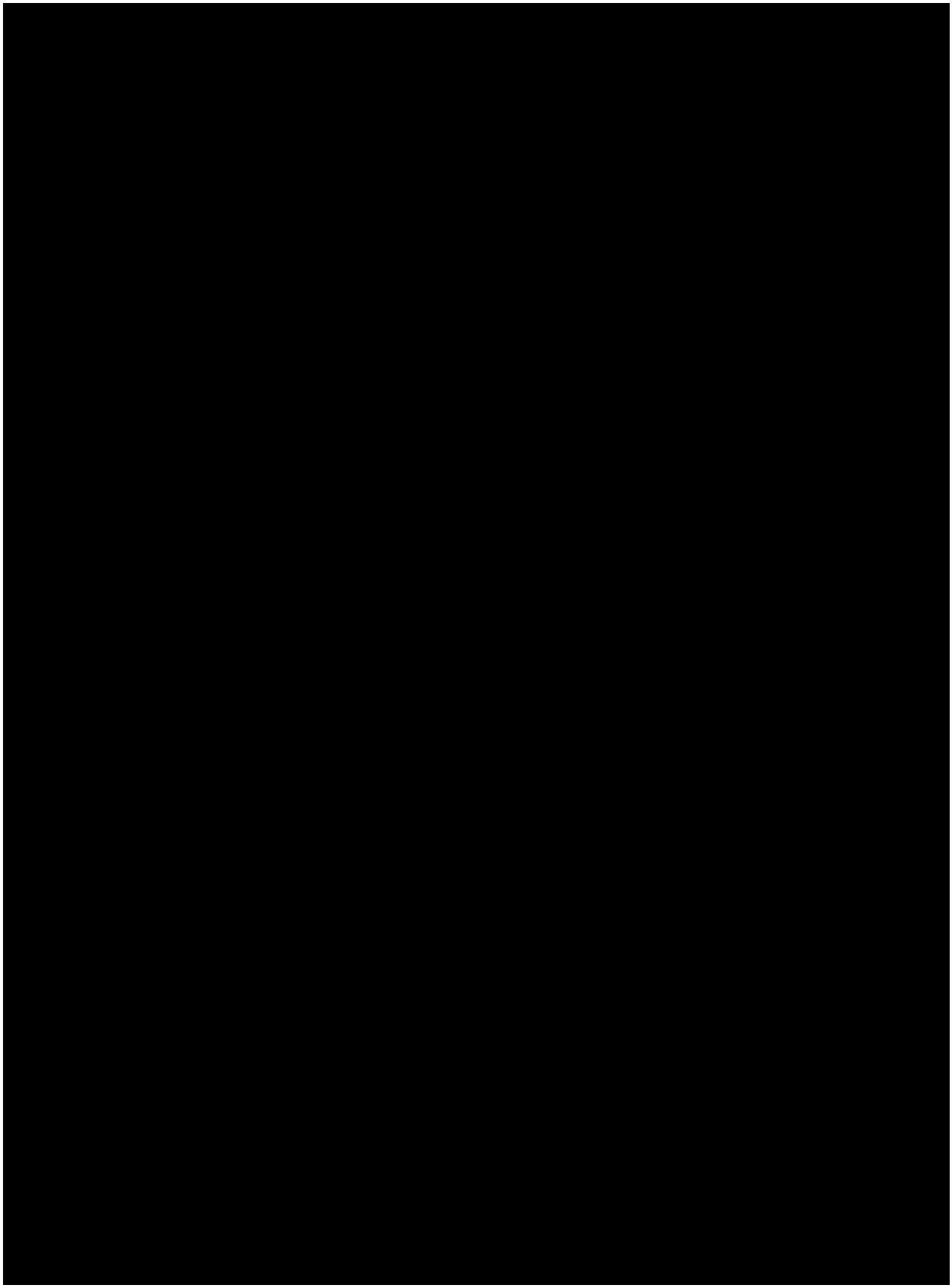


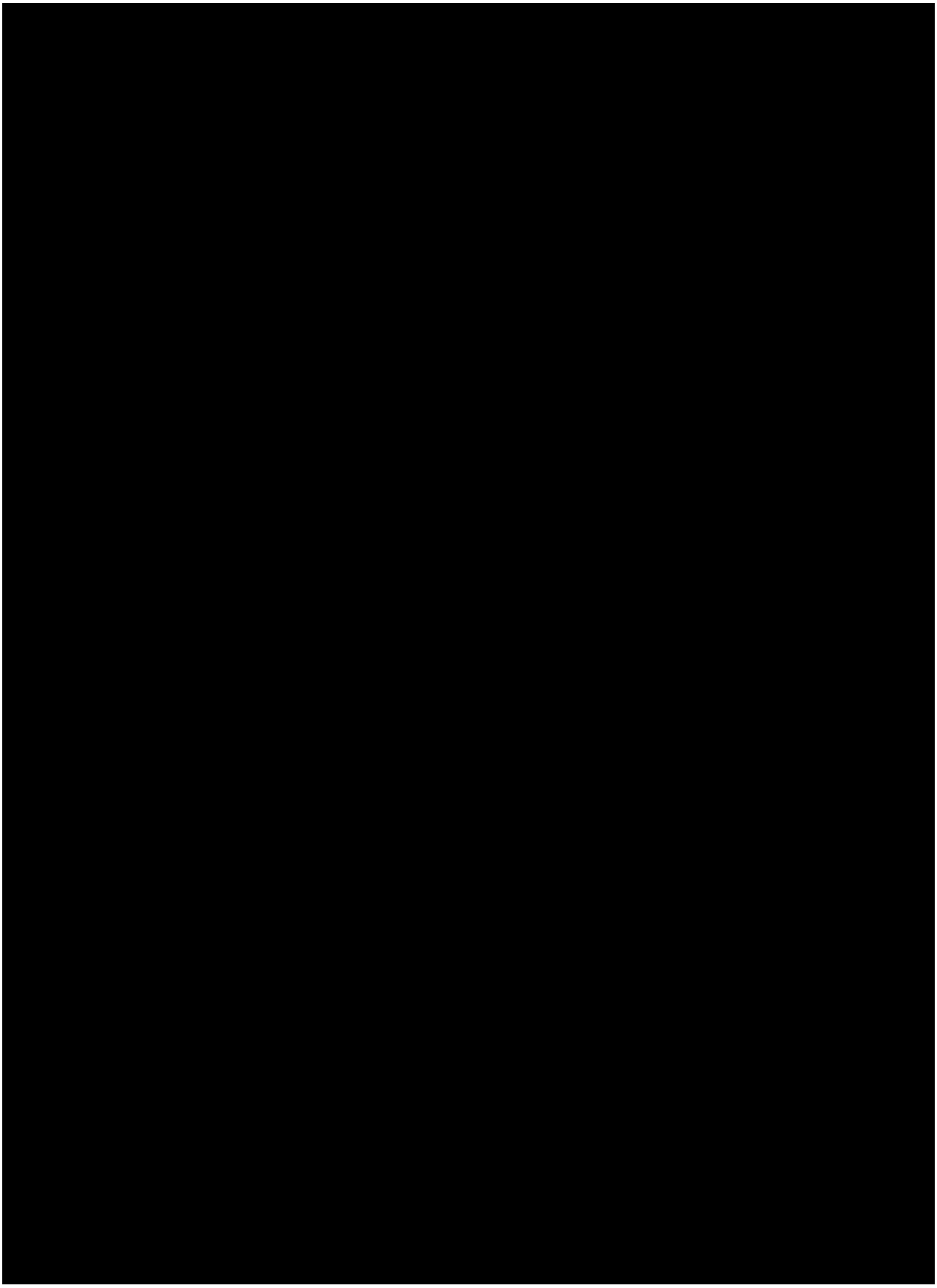


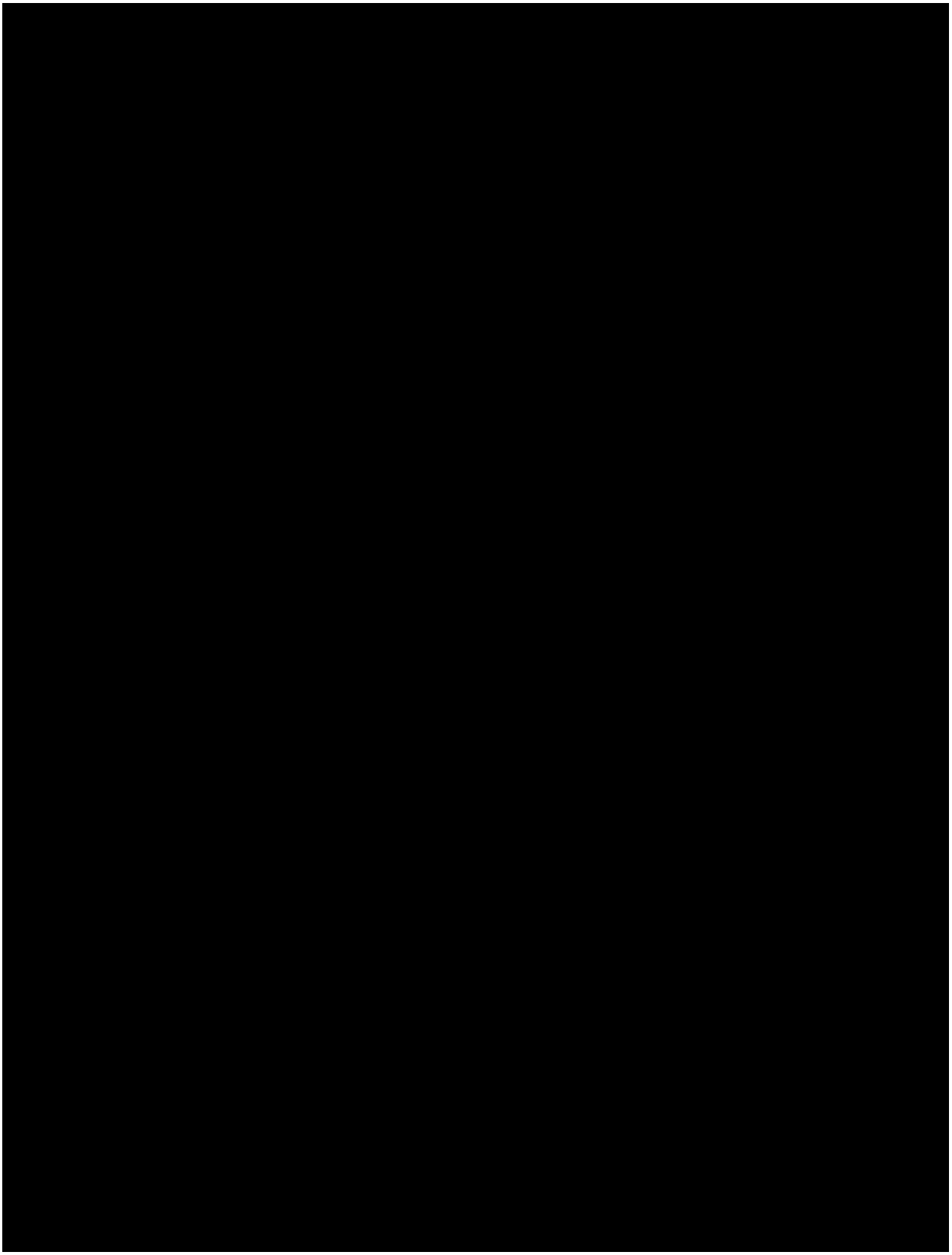


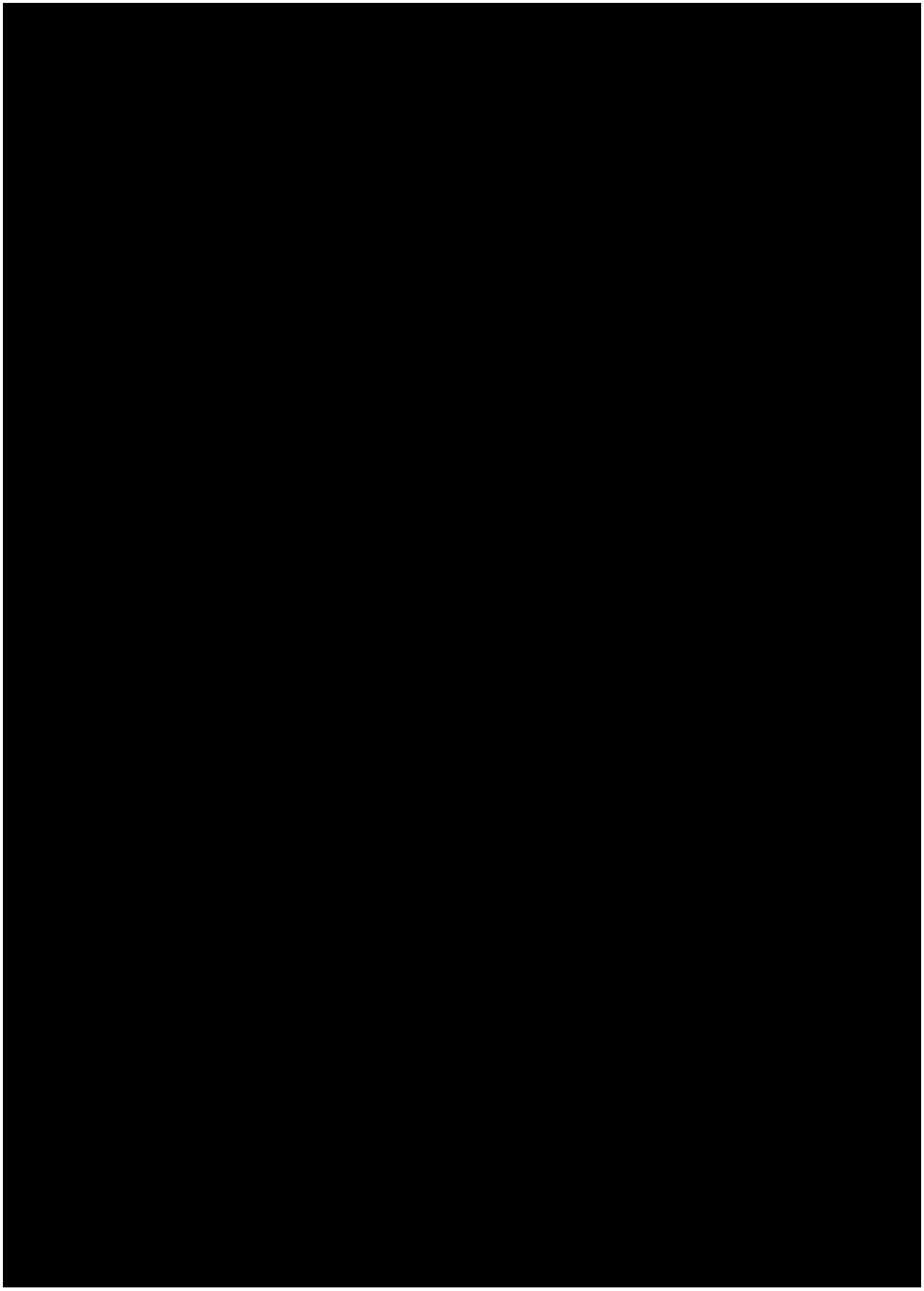












2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
Phase 1b Dose-finding Stage **Primary Objective** • To assess the safety and tolerability of oral AG-120 when administered with subcutaneous (SC) azacitidine and oral AG-221 when administered with SC azacitidine in subjects with newly diagnosed acute myeloid leukemia (AML) with an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive induction chemotherapy (IC). • To establish the recommended combination dose (RCD) of oral AG-120 and oral AG-221 when administered with SC azacitidine. **Phase 1b AG-120 Expansion Stage** **Primary Objective** • To assess the safety and tolerability of oral AG-120 when administered with subcutaneous (SC) azacitidine in subjects with newly diagnosed acute myeloid leukemia (AML) with an IDH1 mutation, who are not candidates to receive intensive induction chemotherapy (IC). **Phase 2 AG-221 Randomized Stage** **Primary Objective** • To assess the efficacy of the combination treatment of oral AG-221 when administered with SC azacitidine compared with SC azacitidine alone in subjects with newly diagnosed AML with an IDH2 mutation, who are not candidates to receive intensive IC.
Secondary Objectives
Phase 1b Dose-finding Stage • To assess the preliminary efficacy of the combination treatments of oral AG-120 when administered with SC azacitidine and oral AG-221 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive IC. **Phase 1b AG-120 Expansion Stage** • To assess the preliminary efficacy of the combination treatment of oral AG-120 when administered with SC azacitidine in subjects with newly diagnosed AML with an IDH1 mutation, who are not candidates to receive intensive IC. • To characterize the pharmacokinetics (PK) of oral AG-120 when administered with SC azacitidine. **Phase 2 AG-221 Randomized Stage** • To evaluate the safety of oral AG-221 when administered with SC azacitidine. • To characterize the pharmacokinetics (PK) of oral AG-221 when administered with SC azacitidine. • To evaluate the effect of oral AG-221 when administered with SC azacitidine versus SC azacitidine alone on health-related quality-of-life (HRQoL) outcomes.

Table 1: Study Objectives (Continued)

[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Phase 1b Dose-finding and AG-120 Expansion Stage			
Primary	Recommended Combination Dose	Review of dose-limiting toxicities (DLTs), safety, PK / pharmacodynamic, biomarker, and preliminary efficacy data by DRT.	Approximately 8 months
	Safety / tolerability	Type, frequency, seriousness and severity of AEs, and relationship of AEs to study treatment.	Approximately 13 months
Secondary	Overall Response Rate (as assessed by the investigator)	Rate of CR + CRi + CRp + MLFS + PR according to modified IWG AML response criteria (Appendix F).	Approximately 13 months
	Sponsor Derived CR and CRh	Rate of CR/ CRh and CR + CRh based on laboratory data	Approximately 13 months

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
[redacted]			
Primary	Overall Response Rate (as assessed by the investigator)	Rate of CR + CRi + CRp + MLFS + PR according to modified IWG AML response criteria (Appendix F).	Approximately 30 months
Secondary	Event-Free Survival	Time from randomization to documented morphologic relapse, progression according to modified IWG AML response criteria (Appendix F), or death from any cause, whichever occurs first.	Approximately 30 months
	Safety / tolerability	Type, frequency, seriousness and severity of AEs, and relationship of AEs to study treatment.	Approximately 30 months
	Complete remission rate	Rate of CR according to modified IWG AML response criteria (Appendix F).	Approximately 30 months
	Sponsor Derived CR	Rate of CR based on laboratory data	Approximately 30 months
	Sponsor Derived CR and CRh	Rate of CR +CRh based on laboratory data	Approximately 30 months
	Hematologic improvement rate	Rate of HI-N + HI-P + HI-E according to IWG MDS HI criteria (Appendix G).	Approximately 30 months
	Duration of Response	Time from the first documented MLFS/CR/CRi/CRp/PR to documented morphologic relapse, progression according to modified IWG AML response criteria (Appendix F), or death due to any cause, whichever occurs first	Approximately 30 months
	Time to response	Time from first dose of study drug to first documented CR/CRi/CRp/ MLFS/PR according to modified IWG AML response criteria (Appendix F)	Approximately 30 months
	Time to sponsored assessed CR and CRh	Time from first dose of study drug to first documented CR / CRh	Approximately 30 months
	Duration of sponsor assessed CR and CRh	Time from the first documented CR/ CRh to documented morphologic relapse, progression	Approximately 30 months
	Overall Survival	Time from randomization to death due to any cause.	Approximately 30 months

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	One-year survival	The probability of survival at 1 year from randomization	Approximately 30 months
	PK parameters	Plasma concentrations and pharmacokinetic parameters of AG-221.	Approximately 30 months
	HRQoL outcomes	European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC QLQ-C30) (Appendix N) and EuroQoL Group EQ-5D-5L instrument (Appendix O)	Approximately 30 months
[redacted]			

Abbreviations: [redacted] AE = adverse event; AML = acute myeloid leukemia; [redacted] 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; DRT = Dose Review Team; EORTC= European Organization for Research and Treatment of Cancer; 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; IWG = International Working Group; MDS = myelodysplastic syndrome; MLFS = morphologic leukemia-free state; [redacted] PK = pharmacokinetics; PR = partial remission; SC = subcutaneous.

3. OVERALL STUDY DESIGN

3.1. Study Design

This Phase 1b/2 study is an open-label, randomized, multicenter trial to evaluate the safety and efficacy of oral AG-120 + SC azacitidine and oral A-221 + SC azacitidine in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively. The study population consists of subjects who are not candidates to receive intensive IC. The study comprises a Phase 1b dose-finding and AG-120 expansion stage and a Phase 2 randomized stage.

Phase 1b Dose-finding Stage

The Phase 1b segment is a combination dose-finding study to identify the RCD of oral AG-120 + SC azacitidine in subjects with an IDH1 mutation or oral AG-221 + SC azacitidine in subjects with an IDH2 mutation. Subjects are considered eligible for this trial if they have newly diagnosed AML and present with co-morbidities, declining performance status, or other factors that in the investigators judgment make them not candidates to receive intensive IC. The Phase 1b segment will evaluate the safety and clinical activity of oral AG-120 or AG-221 administerd with SC azacitidine in this population. For the AG-120 combination, upon declaration of the RCD by the DRT, an AG-120 expansion cohort of up to 15 patients will be enrolled at RCD for further safety evaluation and PK sampling.

The Phase 1b dose-finding segment will use a standard "3 + 3" design. Each dose cohort will enroll a minimum of 3 subjects. Study drug will start on Cycle 1 Day 1 (C1D1) at which time daily dosing will begin for AG-120 and AG-221 for days 1-28 of each 28-day cycle. Azacitidine will be administered SC for 7 days of each 28-day cycle starting at Cycle 1 Day 1. If there are multiple subjects in the screening process at the time the third subject within a cohort begins treatment, up to 2 additional subjects may be enrolled with documented approval of the medical monitor.

The safety of dosing during Phase 1b will be evaluated by the DRT (Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives or designees, as appropriate and all active site investigators and/or designees (at sites with a subject who has received study drug). The DRT will review the emerging safety data from each cohort.

DLT-evaluable Subjects

Dose Determining Set (DDS): Subjects who take at least one dose of study drug in Phase 1b dose-finding stage and either have a DLT during Cycle 1 regardless of amount of study drug exposure, or have no DLT and complete at least 75% of AG-120 or AG-221 doses (21 out of 28 days) and a minimum of 5 doses of azacitidine, and at least 50% of the planned combination doses for AG-120 or AG-221 and azacitidine administered together (in the same day for 4 out of 7 days) in the first 28 days from Cycle 1 Day 1 and are also considered by the Clinical Study Team to have sufficient safety data available to conclude that a DLT does not occur during Cycle 1. A subject diary will be used during outpatient treatment to record details around AG-120 and AG-221 dosing.

Safety Evaluation for Combination Therapy

This study will use a standard "3 + 3" design for AG-120 and AG-221 dose determination, identifying the RCD dose level. Each dose cohort will plan to enroll 3 DLT-evaluable subjects, starting with Dose Level 1. Dose escalation or de-escalation decisions will be made independently for each IDH inhibitor + SC azacitidine therapy. For AG-120, there is no dose escalation, but 1 dose de-escalation is allowed to Dose Level -1. For AG-221, there is 1 dose escalation to Dose Level 2 and 1 dose de-escalation to Dose Level -1. Due to the lack of overlapping toxicities, azacitidine will be administered, by the site staff, at 75 mg/m^2 dose for 7 days of the 28 day cycle. The DRT will review all safety data available for each cohort to determine whether a dose adjustment of azacitidine is warranted for the combination.

Phase 1b AG-120 Expansion Stage

An expansion cohort of approximately 15 IDH1 patients will be enrolled to the AG-120 combination (Section 3.1.1.4). Subjects enrolled in the AG-120 expansion will receive the AG-120 + azacitidine at the RCD.

Phase 2 Randomized Stage

The Phase 2 segment of the study is an open label, randomized, 2-arm design to evaluate the efficacy and safety of oral AG-221 with SC azacitidine versus SC azacitidine alone. Eligible subjects must have newly diagnosed AML with an IDH2 mutation and, who are not candidates to receive intensive IC based on the investigators assessment.

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.

- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up or disease progression will continue to be assessed during the Follow-up period of the study for response until disease progression (Section 6.3).
- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up will continue to be assessed for subsequent AML therapies, and survival (Section 6.3).

The trial will continue until enough EFS events to allow full statistical analysis (Section 9).

See Figure 3: Overall Study Design Phase 1b and Figure 4: Overall Study Design Phase 2.

3.1.1. Phase 1b Dose-finding and AG-120 Expansion Stage

The Phase 1b segment of the study will consist of Screening, Treatment, and Follow-up periods.

The dose finding will use a "3 + 3" design (Figure 3). Each dose cohort will plan to enroll 3 subjects. Both investigational products will be started on Cycle 1 Day 1 (C1D1).

In the AG-120 dose-finding arm, a minimum of 3 eligible subjects with an IDH1 mutation will be enrolled into Cohort 1 with oral AG-120, 500 mg daily and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle. If none of the 3 subjects has a DLT then the RCD will be confirmed by the DRT. An additional 3 subjects will be enrolled if 1

subject has a DLT. If 2 or more DLTs are declared in Cohort 1, then Cohort -1 will be explored with AG-120 at a dose of 250 mg daily and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle (Table 3). If a cohort is expanded to six subjects due to a DLT the RCD will be declared by the DRT at the dose level where no more than 1 of six subjects experiences a DLT (Figure 1). Upon declaration of the RCD by the DRT an AG-120 expansion cohort of up to 15 patients will be enrolled for further safety evaluation and PK sampling.

For AG-221 two dose levels will be explored. Three eligible subjects with an IDH2 mutation will be enrolled into Cohort 1 and receive oral AG-221, 100 mg daily and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle. If no DLTs are observed in a cohort of 3 subjects, or no more than 1 DLT in an expanded cohort of 6 subjects experience a confirmed DLT the RCD will be confirmed by the DRT and the 100 mg dose will be used as the starting dose for the Phase 2 segment of the study. Dose escalation to Cohort 2 will be initiated with oral AG-221 200 mg once a day and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle to explore the tolerability of the combination at this dose level. If 2 or more subjects in the expanded Cohort 1 experience a DLT, Cohort -1 with oral AG-221 50 mg daily and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle will be explored and no escalation to Cohort 2 or dose escalation to a 200 mg dose will be used in Phase 2 of this study (Figure 2).

The RCD will be declared as Cohort -1 if no DLTs are observed in a cohort of 3 subjects, or no more than 1 DLT in an expanded cohort of 6 subjects.

If enrollment is initiated in Cohort 2 and no DLTs are observed in a cohort of 3 subjects, or no more than 1 DLT in an expanded cohort of 6 subjects, the data will be reviewed by the DRT for potential dose escalation during Phase 2 to augment treatment response.

Table 3: Phase 1b Dose Cohorts

	IDH1		IDH2	
Cohort	**AG-120**	**Azacitidine**	**AG-221**	**Azacitidine**
Cohort -1	250 mg QD for 28 days	75 mg/m^2/day SC for 7 days of each 28-day cycle	50 mg QD for 28 days	75 mg/ m^2/day SC for 7 days of each 28-day cycle
Cohort 1	500 mg QD for 28 days	75 mg/m^2/day SC for 7 days of each 28-day cycle	100 mg QD for 28 days	75 mg/ m^2/day SC for 7 days of each 28-day cycle
Cohort 2	NA	NA	200 mg QD for 28 days	75 mg/ m^2/day SC for 7 days of each 28-day cycle

The DRT will review all toxicities following the completion of Cycle 1 of each cohort to determine whether dose modification of azacitidine is warranted or additional cohorts are needed to further assess the safety of the combination.

3.1.1.1. 3 + 3 Design

The 3 + 3 design allows for the enrollment of three subjects concurrently, with IDH1 or IDH2 mutations, into their respective Cohort 1. Local confirmation of the primary malignancy is required. Subjects in the dose-finding phase are required to have IDH1 or IDH2 gene-mutated disease, documented by local site testing.

The dose-finding phase will use a standard "3 + 3" design. During the dose-finding phase, eligible subjects with an IDH 1 mutation will be enrolled into one cohort of AG-120, or for subjects with an IDH2 mutation, sequential cohorts of increasing doses of AG-221. Each dose cohort will plan to enroll a minimum of 3 subjects. A cohort will be expanded to 6 subjects if one of the initial 3 subjects experiences a DLT. If there are multiple subjects in the screening process at the time the third subject within a cohort begins treatment, up to 3 additional subjects may be enrolled, for a maximum of 6 subjects per cohort, with documented approval of the Medical monitor.

An expansion cohort of approximately 15 IDH1 patients will be enrolled to the AG-120 combination (Section 3.1.1.4).

Schematics for the dose finding for doses of AG-120 and AG-221 are provided in Figure 1 and Figure 2.

AG-120

The safety of dosing will be evaluated by the DRT comprised of the Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives or designees, as appropriate, and all active site investigators and/or designees (at sites with a subject who has received study drug). The DRT will review the emerging safety data from the cohort to determine whether dose de-escalation will occur.

AG-120 Cohort 1

If, after the third subject in Cohort 1 completes the 28-day DLT evaluation period (ie, Cycle 1), no DLTs (Section 3.1.1.3) are observed, Cohort 1 will be declared the RCD following review by the DRT.

If 1 of 3 subjects experiences a DLT during the first cycle, 3 additional subjects will be enrolled in that cohort. If none of the additional 3 subjects experience a DLT, the RCD will be confirmed following review by the DRT.

AG-120 de-escalation from Cohort 1 to Cohort -1

If 2 or more subjects in Cohort 1 experience DLTs during the first cycle, dose escalation will be halted and the next lower dose level (Cohort -1) will be explored. If no DLTs are observed, Cohort -1 will be declared the RCD by the DRT.

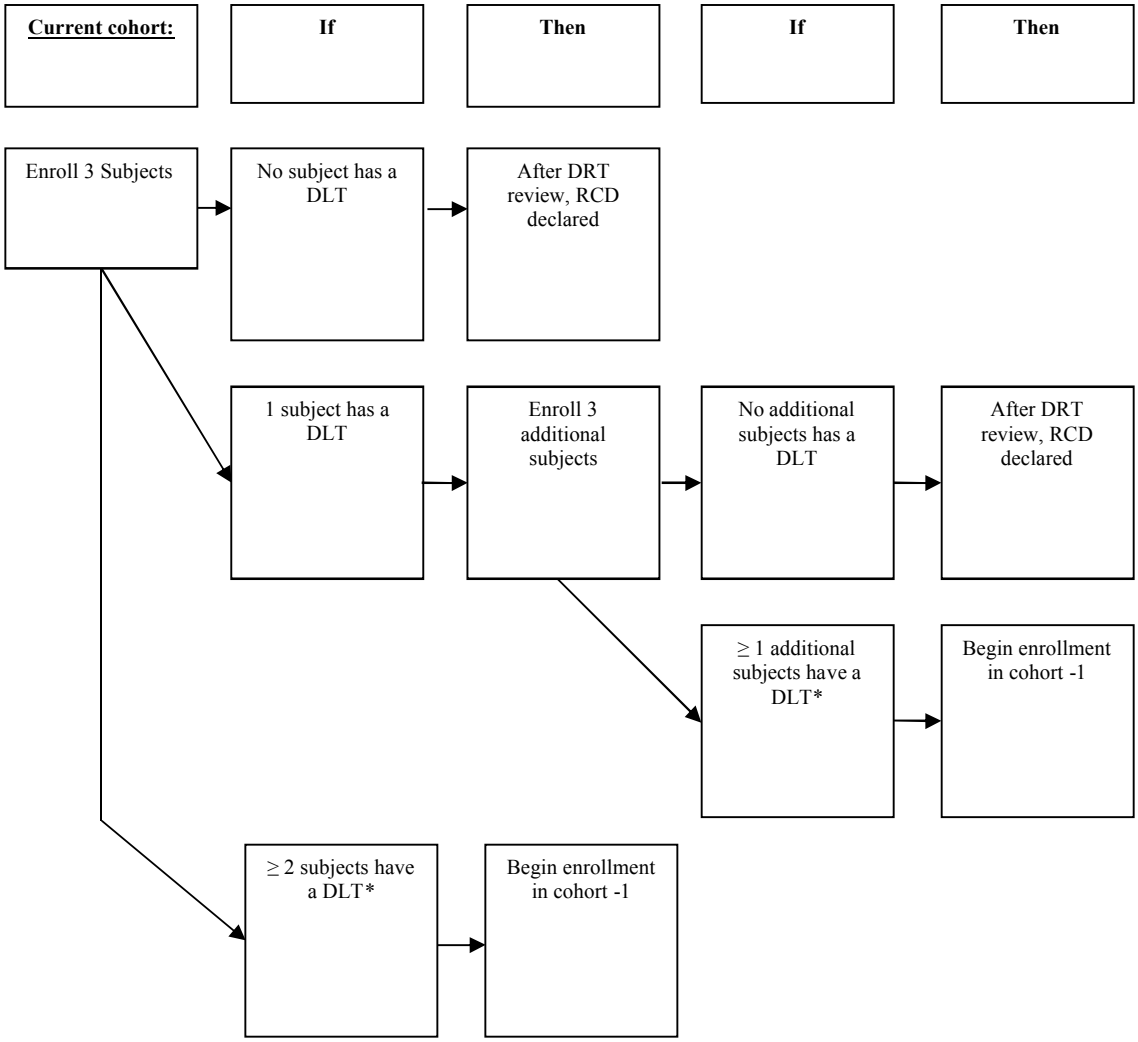
If 1 of 3 subjects experiences a DLT in Cohort -1, 3 additional subjects will be enrolled in that cohort. If none of the additional 3 subjects experience a DLT, the expanded Cohort 1 will be declared the RCD and will be confirmed following DRT review.

If 2 or more subjects in Cohort -1 experience DLTs during the first cycle, dosing will be halted and all data will be reviewed by the DRT.

Note that if a given cohort initially enrolled 4 or 5 subjects (ie, if there were multiple subjects in the screening process at the time the third subject within a cohort began treatment), the same rules for dose de-escalation apply. If 1 of the 4 (or 5 subjects) experiences a DLT, the cohort will be expanded to include a total of 6 subjects, and will be halted if 2 or more subjects experience a DLT.

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

Figure 1: AG-120 Dose-finding Scheme



* If cohort is -1, dosing will be halted for review.
Note: DRT = Dose Review Team; DLT = dose-limiting toxicity; RCD = recommended combination dose.

AG-221

The safety of dosing will be evaluated by the DRT comprised of the Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives or designees, as appropriate and all active site investigators and/or designees (at sites with a subject who has received study drug). The DRT will review the emerging safety data from each cohort to determine whether dose escalation or dose de-escalation will occur.

AG-221 escalation from Cohort 1 to Cohort 2

If no DLTs are observed in a cohort of 3 subjects, or no more than 1 DLT in an expanded cohort of 6 subjects experience a confirmed DLT the RCD will be confirmed by the DRT and the 100 mg dose will be used as the starting dose for the Phase 2 segment of the study. Dose escalation to Cohort 2 will also be initiated with oral AG-221 200 mg once a day and azacitidine 75 mg/m^2/day SC for 7 days of each 28-day cycle starting on Day 1 of each cycle to explore the tolerability of the combination at this dose level.

If enrollment is initiated in Cohort 2 and no DLTs are observed in a cohort of 3 subjects, or no more than 1 DLT in an expanded cohort of 6 subjects the data will be reviewed by the DRT for potential dose escalation during Phase 2 to augment treatment response. After Cycle 1, dose interruptions and reductions are allowed to alleviate toxicity as described in Section 7.2.2.3.1 and Section 7.2.2.3.4, and no re-escalation will be allowed.

AG-221 de-escalation from cohort 1 to cohort -1

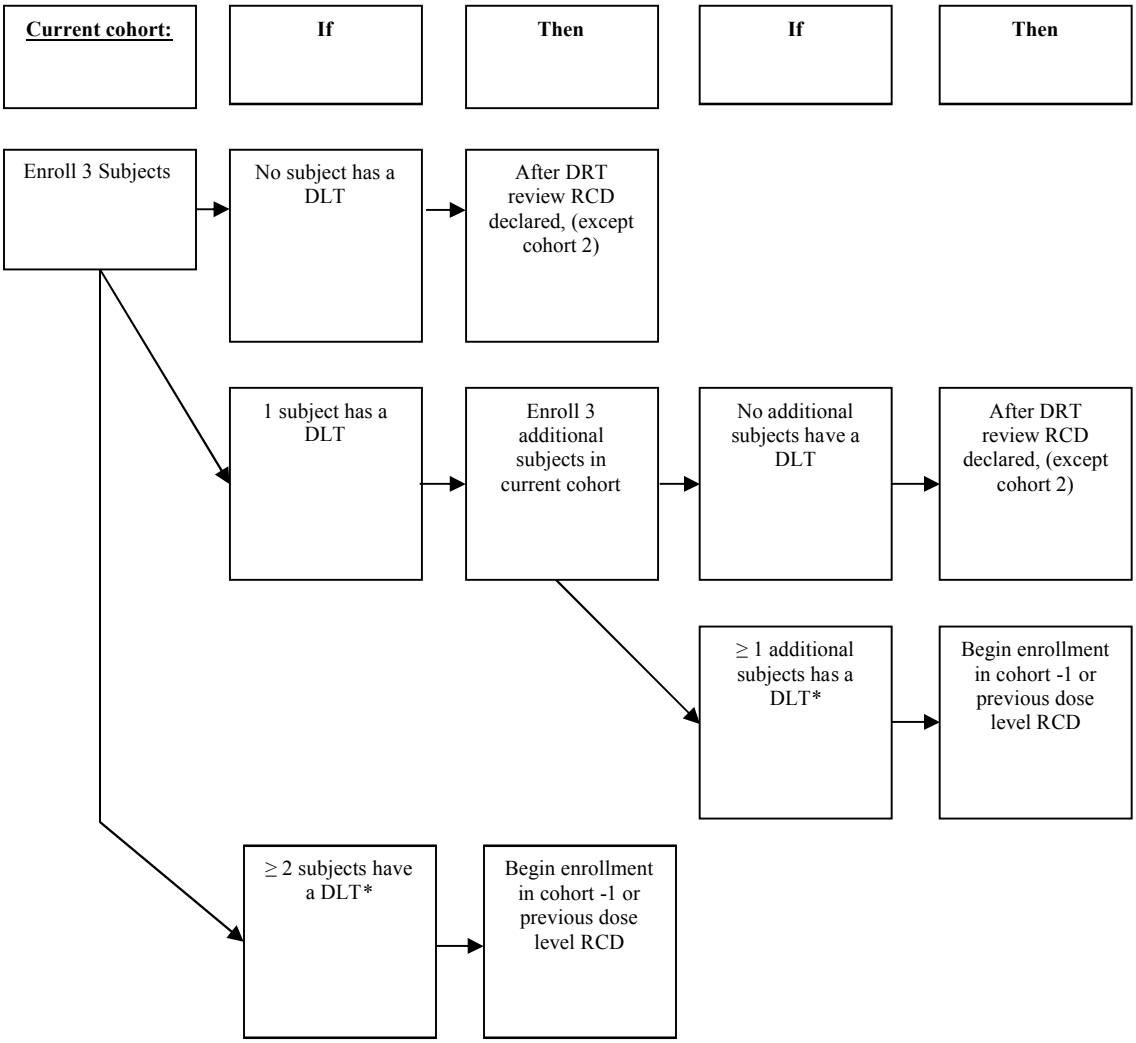
If 2 or more subjects in cohort 1 experience DLTs during the first cycle, dose escalation will be halted and following review by the DRT, the next lower dose level (cohort -1) will be explored. If no DLTs are observed (see 3.1.1.3) cohort -1 will be declared the RCD following DRT review.

If 1 of 3 subjects experiences a DLT in cohort -1, 3 additional subjects will be enrolled in that cohort. If none of the additional 3 subjects experience a DLT in the expanded cohort -1 it will be declared the RCD will be confirmed following DRT review.

If 2 or more subjects in cohort -1 experience DLTs during the first cycle, dosing will be halted and all data will be reviewed by the DRT.

Note that if a given cohort initially enrolled 4 or 5 subjects (ie, if there were multiple subjects in the screening process at the time the third subject within a cohort began treatment), the same rules for dose escalation apply. If 1 of the 4 (or 5 subjects) experiences a DLT, the cohort will be expanded to include a total of 6 subjects; dose escalation will occur if only 1 of 6 subjects experiences a DLT and will be halted if 2 or more subjects experiences a DLT.

Figure 2: AG-221 Dose-finding Scheme



* If cohort is -1, dosing will be halted for review.
Note: DRT = Dose Review Team; DLT = dose-limiting toxicity; RCD = recommended combination dose.

Azacitidine

Azacitidine will be administered at the standard dose of 75 mg/m^2/day SC for 7 days of each 28-day cycle. The DRT will review all toxicities following the completion of Cycle 1 to determine whether dose modification of azacitidine is warranted or additional cohorts are needed to further assess the safety of the combination.

When all subjects have completed at least the first 28-day cycle, the DRT will meet and review all Phase 1b segment safety data to determine the starting doses of the AG-120 or AG-221 administered with azacitidine to be used in the treatment arms of the randomized Phase 2 segment of the study.

All subjects enrolled into the Phase 1b segment of the study may continue to receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study.

A Phase 1b DLT is defined in Section 3.1.1.3.

Due to frequent co-morbidities and concurrent medications in the population under study, attribution of AEs to a particular drug is challenging. Therefore, all AEs that cannot clearly be determined to be unrelated to AG-120 or AG-221 will be considered relevant to determining DLTs and will be reviewed by the DRT.

The DRT also will review any other emergent toxicities that are not explicitly defined by the DLT criteria to determine whether any warrant a DLT designation.

3.1.1.2. Dose Review Team (DRT)

The DRT consists of the Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives or designees, as appropriate and all active site investigators and/or designees (at sites with a subject who has received study drug).

The DRT members are responsible for dosing decisions for the study. Dosing decisions may include escalation to the next planned dose, de-escalation to a lower dose, or evaluation of alternative dose levels for individual subjects. All available safety and preliminary efficacy data will be reviewed and can be considered in the DRT's decisions when a cohort has completed 28 days.

3.1.1.3. Phase 1b Dose Limiting Toxicity

Toxicity severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. DLTs will be defined as any of the following events that commence within 28 days of the first dose of IP in a 28-day treatment cycle, constitute a change from baseline irrespective of outcome and are determined by the investigator to be related to treatment.

Dose-limiting toxicities for the RCD will be evaluated during the first 28 day cycle for subjects enrolled into the dose-escalation phase of the study. The DLT evaluation period will begin at the time the subject receives one dose of the assigned treatment.

DLTs will be defined as;

Hematologic toxicities:

While AG-120 and AG-221 are not associated with myelosuppression, azacitidine has a well characterized association with cytopenias and other hematologic toxicities. For the Phase 1b portion, hematologic toxicities will not be considered as a DLT for AG-120/221 and will be mitigated through dose modification of azacitidine in subsequent cycles. The DRT will review hematology lab data at the completion of each cohort to determine whether any warrant a DLT designation.

Non-hematologic:

All clinically significant non-hematologic toxicities CTCAE ≥ Grade 3 with the exception of:

- ≥ Grade 3 blood bilirubin increases in subjects receiving AG-221 with a uridine diphosphate-glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) mutation treated with AG-221. In subjects receiving AG-221 with a UGT1A1 mutation, blood bilirubin increases of >5× upper limit of normal (ULN) may be considered a DLT.
- Any non-hematologic Grade 3 laboratory abnormality that is asymptomatic and rapidly reversible (ie, returns to ≤ Grade 1 within 4 days) and does not recur with continuation or resumption of treatment.
- Grade 3 anorexia, diarrhea, nausea or vomiting lasting < 72 hours with optimal medical management.
- Grade 3 fatigue, which resolves to Grade ≤ 2 within 4 days and does not recur at the same severity with continuation or resumption of treatment.

Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition.

3.1.1.4. Phase 1b AG-120 Expansion Stage

Upon declaration of the RCD by the DRT an expansion cohort of up to 15 patients will be enrolled for further safety evaluation and PK sampling (Section 6.6).

3.1.1.5. Phase 1b Screening Period

Informed consent must be obtained prior to any study-specific procedures being performed. Subjects who meet all eligibility criteria and have completed all screening procedures may be enrolled into the study. Screening assessments must be completed within 28 days prior to the first dose of study treatment, depending on the specific assessment, as outlined in the Table 4: Table of Events.

Local confirmation of the primary malignancy is required. Subjects in the dose escalation phase are required to have IDH1 or IDH2 gene-mutated disease, documented by local site testing.

3.1.1.6. Phase 1b Treatment Period

Eligible subjects will report to the study site to receive study treatment and protocol-specified procedures according to the Table 4: Table of Events. The treatment period will consist of continuous 28-day cycles.

Subjects with newly diagnosed AML who are deemed by the investigator not candidates to receive intensive IC will be assigned to oral AG-120 + SC azacitidine or oral AG-221 + SC azacitidine depending on the IDH mutations (IDH1 or IDH2, respectively).

The discontinuation of AG-120, AG-221, or azacitidine for subjects in the combination arms of the study is allowed. Subjects may continue treatment with single agent AG-120, AG-221, or azacitidine if in the investigator's assessment the subject continues to show clinical benefit and all protocol-specified criteria for continuing study treatment are met.

All subjects may continue to receive study treatment until disease progression or unacceptable toxicity, withdrawal of consent, or end of the study. Subjects assigned to a lower dose cohort will

continue at their assigned dose throughout their participation in the study; dose escalation up to the RCD dose is not permitted.

3.1.1.7. Phase 1b End of Treatment Visit

Subjects are to return to the study site for the End of Treatment Visit assessment within 7 (±3) days after discontinuation of all study treatment (Table 4: Table of Events).

3.1.1.8. Phase 1b Follow-up Period

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.

- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up or disease progression will continue to be assessed during the Follow-up period of the study for response until disease progression, relapse, or the start of second line therapy (Section 6.3).
- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up will continue to be assessed for subsequent AML therapies, and survival (Section 6.3).

3.1.2. Phase 2 AG-221 Randomization Stage

The Phase 2 segment of the study will consist of Screening, Treatment, and Follow-up periods. Refer to (Figure 4: Overall Study Design Phase 2) for the study design. All subjects randomized will be stratified by primary (ie, de novo) or secondary (progression of MDS or myeloproliferative neoplasms [MPN], or therapy-related) AML according to the WHO classification (Appendix B).

3.1.2.1. Phase 2 Screening Period

Informed consent must be obtained prior to any study-specific procedures being performed. Subjects who meet all eligibility criteria and have completed all screening procedures may be enrolled into the study. The diagnosis of AML will be performed locally for enrollment and confirmed based on a subsequent central pathology review. IDH mutational status will be assessed locally; for sites without local testing capabilities, a referral lab will be identified. A bone marrow aspirate and peripheral blood sample must be sent [redacted] to the central lab for potential retrospective confirmation of mutational status. Inclusion in the trial can be based on local IDH testing. Screening assessments must be completed within 28 (+ 3) days prior to the first dose of study treatment, depending on the specific assessment, as outlined in the Table 4: Table of Events.

3.1.2.2. Phase 2 Treatment Period

Eligible subjects will report to the study site to receive study treatment and protocol-specified procedures according to the Table 4: Table of Events. The treatment period will consist of continuous 28-day cycles.

Following the determination of the RCD subjects with newly diagnosed AML who are deemed by the investigator not candidates to receive intensive IC will be randomized 2:1 to one of the following arms:

IDH2 Subjects

Arm 1: Oral AG-221 + SC azacitidine (66 Subjects)

Arm 2: SC azacitidine (33 Subjects)

Dose modifications and interruptions are permitted as detailed in Sections 7.2.2.3.1 and 7.2.2.3.4.

The discontinuation of AG-221 or azacitidine for subjects in the combination arms of the study is allowed. Subjects may continue treatment with single agent AG-221 or azacitidine if in the investigator's assessment the subject continues to show clinical benefit and all protocol-specified criteria for continuing study treatment are met.

3.1.2.3. Phase 2 End of Treatment Visit

Subjects are to return to the study site for the End of Treatment Visit assessment within 7 (±3) days after discontinuation of all study treatment (Table 4: Table of Events).

3.1.2.4. Phase 2 Follow-up Period

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.

- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up or disease progression will continue to be assessed during the Follow-up period of the study for response until disease progression, relapse, or the start of second line therapy (Section 6.3).
- All subjects discontinued from study treatment for any reason except withdrawal of consent for follow-up will continue to be assessed for subsequent AML therapies, and survival (Section 6.3).

3.1.2.5. Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) with multi-disciplinary representation will evaluate safety in compliance with a prospective charter that contains the details of the DMC responsibilities, authorities and procedures.

[redacted]

Figure 3: Overall Study Design Phase 1b Dose-finding and AG-120 Expansion Stage

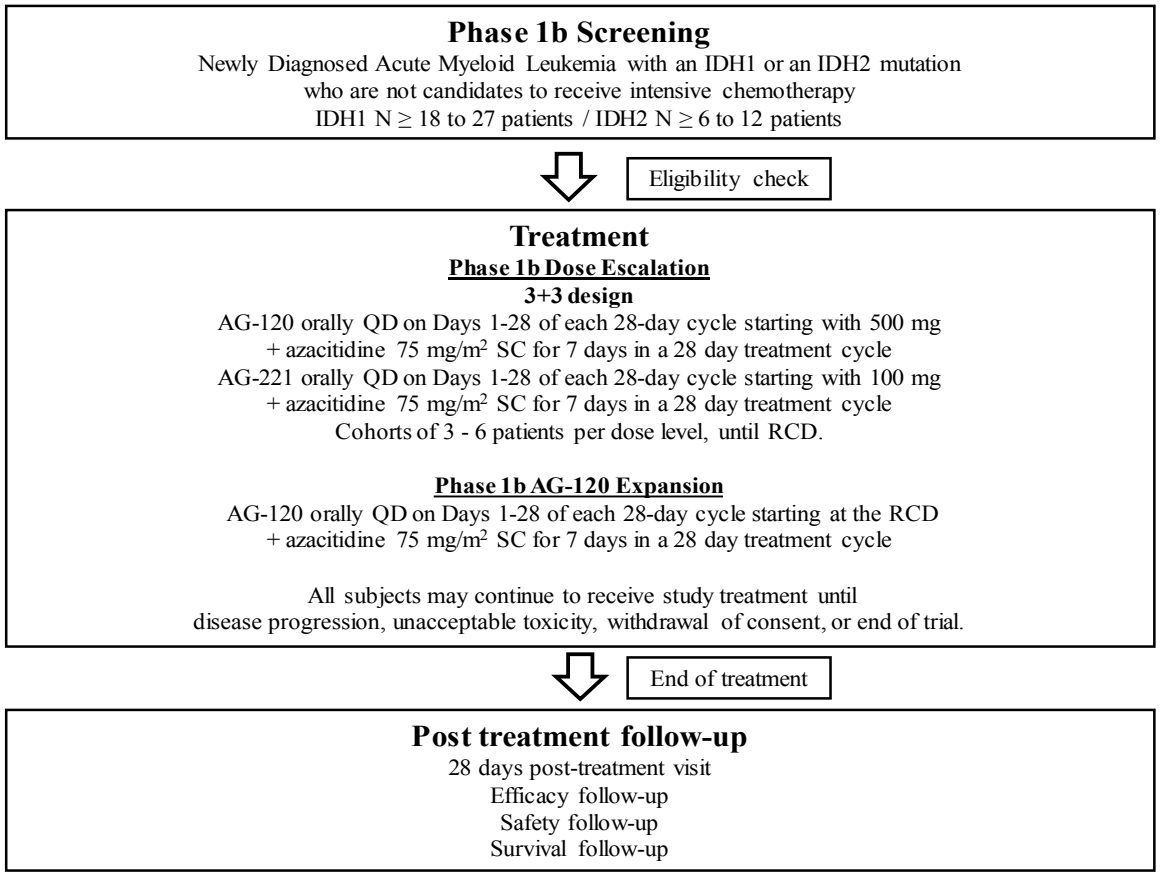
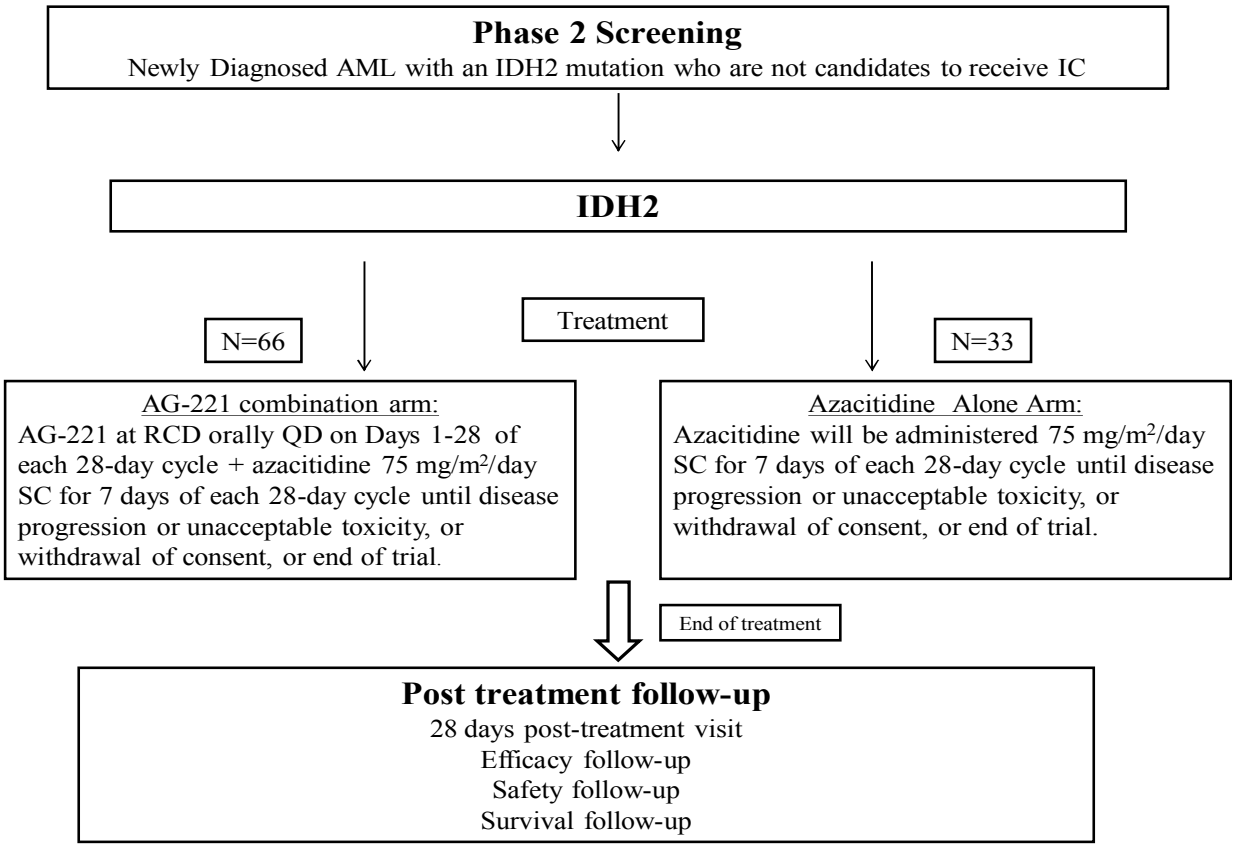


Figure 4: Overall Study Design Phase 2 AG-221 Randomization Stage



3.2. Study Duration for Subjects

For a single subject, the expected duration of the study is 30 months, including a screening period for up to 28 days, inclusive of overall survival.

The study will conclude once the subjects have died, are lost to follow up, withdrew consent, or have discontinued from the study (Section 11.2).

3.3. End of Trial

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

4. STUDY POPULATION

4.1. Number of Subjects

It is estimated that approximately 39 subjects will be enrolled during Phase 1b and approximately 99 subjects in Phase 2. In Phase 1b subjects must have newly diagnosed AML with a confirmed IDH 1 or 2 gene mutation and, per the investigator, not be candidates to receive intensive IC. In Phase 2 subjects must have newly diagnosed AML with a confirmed IDH2 mutation and, per the investigator, not be candidates to receive intensive IC.

4.2. Inclusion Criteria

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

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject has newly diagnosed, primary (ie, de novo) or secondary (progression of MDS or myeloproliferative neoplasms [MPN], or therapy-related) AML according to the WHO classification (Appendix B) with ≥ 20% leukemic blasts in the bone marrow:
   a. Have an IDH1 or IDH2 gene mutation (R132, R140, or R172)
      - IDH mutational status will be assessed locally; for sites without local testing capabilities, a referral lab will be identified
   b. By the investigator's assessment who are not candidates to receive intensive IC
5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (Appendix D).
6. Subject has adequate organ function defined as:
   - Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 3 x ULN, unless considered due to leukemic organ involvement.
   - Serum total bilirubin < 1.5 x ULN. Higher levels are acceptable if these can be attributed to ineffective erythropoiesis, ≤ 3 times the upper limit of normal for Gilbert's syndrome (eg, a gene mutation in UGT1A1), or leukemic organ involvement.
   - Serum creatinine < 2 x ULN or creatinine clearance > 30 mL/min based on the Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR):

     $GFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.212\ \text{if African American})$
7. Agree to serial bone marrow aspirate/biopsies.

8. 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 a vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the FCBP trial participant and that a vasectomized partner has received medical assessment of the surgical success]) at screening and throughout the study, and for at least 4 months following the last study treatment; 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 Period (note that the screening serum pregnancy test can be used as the test prior to the start of study treatment in the Treatment Period if it is performed within the 72-hour timeframe).
9. Male subjects must agree to practice true abstinence from sexual intercourse or agree to the use of highly effective contraceptive methods (as described above) with non-pregnant female partners of child bearing 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 at least 4 months following the last study treatment (6 months following last dose of azacitidine in Canada).

   Furthermore, the male subject must agree to use a condom while treated with azacitidine and for at least 4 months following the last azacitidine dose.

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).

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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 bilateral salpingectomy (surgical removal of both Fallopian tubes) or 2) at age >45 years 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 (LAM) are not considered to be acceptable methods of contraception.

3. Subject has received a targeted agent against an IDH1 or IDH2 mutation.
4. Subject has received prior systemic anticancer therapy, HSCT, or radiotherapy for AML. Note: Hydroxyurea is allowed prior to enrollment for the control of peripheral leukemic blasts in subjects with leukocytosis. (however, hydroxyurea should not be given within 72 hours prior to and after administration of azacitidine). For subjects with secondary AML (eg, MDS or MPN) treatment for prior cancer is not exclusionary; full treatment information will be collected within the CRF. The use of all trans retinoic acid (ATRA) for suspected APL is not exclusionary provided it is discontinued prior to initiation of treatment in the protocol.
5. Subject has received more than 1 cycle of prior treatment with azacitidine, or subject has received any prior treatment with decitabine for MDS.

   Clarification: Subjects with newly diagnosed AML who are currently receiving their 1st cycle of azacitidine (7 days) can be screened for the study. On study, Cycle 1 must be started at 28 days (+/- 3 days) after initiation of the pre-study azacitidine.
6. 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.
7. Subject has immediate life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation.
8. 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.
9. 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)
10. Subject is known seropositive for or has active viral infection with human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)
11. Subject is known to have dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally

12. Subject has uncontrolled hypertension (systolic blood pressure [BP] > 180 mmHg or diastolic BP > 100 mmHg)
13. 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: phenytoin (CYP2C9), S-mephenytoin (CYP2C19), thioridazine (CYP2D6), theophylline, and tizanidine (CYP1A2) (Appendix K).
14. Subject is taking the breast cancer resistance protein (BCRP) transporter-sensitive substrate rosuvastatin; subject should be excluded from the study unless he/she can be transferred to other medications at least 5 half-lives prior to the start of study treatment (Appendix L).
15. 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).
16. Subject has known or suspected hypersensitivity to any of the components of study therapy.
17. Subject is taking medications that are known to prolong the QT interval (Appendix M) unless he/she can be transferred to other medications within ≥ 5 half-lives prior to the start of study treatment. (If equivalent medication is not available, QTc will be closely monitored as defined in Section 8.1.)
18. 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.
19. Female subject who is pregnant or lactating.
20. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
21. Subject has any condition, including the presence of laboratory abnormalities, that places the subject at unacceptable risk if he/she were to participate in the study.
22. Subject has any condition that confounds the ability to interpret data from the study.

5. TABLE OF EVENTS

Table 4: Table of Events

Events Table covers both Phase 1b & 2 (unless otherwise noted)	Screening Period	Treatment Period[a]								Follow-up Period[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]	-	-	-	-	-	-	-	-	-
IWRS Subject Status Registration (Phase 1b/2)	×	× [d]	-	-	-	×	-	×	×	-
Inclusion & Exclusion Criteria	×	× [e, f]	-	-	-	-	-	-	-	-
Demographics	×	-	-	-	-	-	-	-	-	-
AML Diagnosis	× [g]	-	-	-	-	-	-	-	-	-
Local Testing of IDH1/ IDH2 Gene Mutations on BMA and PB (In addition, BMA and PB samples to be sent to central lab)	× [g]	-	-	-	-	-	-	-	-	-
Medical History	×	-	-	-	-	-	-	-	-	-
Prior Medications and Procedures	× [h]	-	-	-	-	-	-	-	-	-
EORTC QLQ-C30 and EQ-ED-5L	-	×	-	-	-	×	-	×	×	-
ECOG Performance Status	×	×	-	-	-	×	-	×	×	-
Physical Examination [i]	×	×	-	-	-	×	-	×	×	-
Vital Signs	×	×	×	×	×	×	×	×	×	-

Table 4: Table of Events (Continued)

Events Table covers both Phase 1b & 2 (unless otherwise noted)	Screening Period	Treatment Period[a]								Follow-up Period[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		
ECHO / MUGA Scan [k]	× [l]	As clinically indicated								-
Height	×	-	-	-	-	-	-	-	-	-
Body Weight	×	×	-	-	-	×	-	×	×	-
BSA Calculation [j]	×	×	-	-	-	×	-	×	-	-
12-Lead ECG [k]	×	×	-	×	-	×	-	×	×	-
Pregnancy Test (FCBP only) [m]	× [n]	× [k, o]	-	-	-	× [k]	-	× [k]	× [k]	-
Urinalysis [n]	×	As clinically indicated								-
Coagulation Laboratory [n]	×									-
Hematology Laboratory [n]	×	×	×	×	×	×	×	×	×	× [p]
Chemistry Laboratory [n]	×	×	-	×	-	×	-	×	×	-
UGT1A1 Gene Mutation Test (for diagnosis of Gilbert's Syndrome; refer to Section 4.2) [n]	×	-	-	-	-	-	-	-	-	-
Cardiac Markers [n]	-	× [f]	× [q]							-
Fasting Lipid Panel [n]	-	× [f]	× [r]							-
Adverse Event	× [s]									

Table 4: Table of Events (Continued)

Events Table covers both Phase 1b & 2 (unless otherwise noted)	Screening Period	Treatment Period[a]								Follow-up Period[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		
Concomitant Medications and Procedures	**Continuous until 28 days after the last study treatment**									
Transfusion Data Collection and Assessment [t]	**Assess and record on an ongoing basis (prior to each dose of IP) until the next 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. Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.**									
[redacted]										
BMA for Disease Assessment [v, g]	×	× [w]	-	-	-	× [x]	-	× [y]	× [z]	× [p]
[redacted]										
Blood for Pharmacodynamics [redacted] [g, v]	×	×	-	×	-	× [x]	-	× [y]	× [z]	× [p]
[redacted]										
BMB [g, bb]	×	× [w]	-	-	-	× [x]	-	× [y]	× [z]	× [p]
PB Smear [g]	×	× [w]	-	-	-	× [x]	-	× [y]	× [z]	× [p]
Cytogenetics Testing [g]	×	× [w, cc]	-	-	-	× [x, cc]	-	× [y, cc]	× [z, cc]	× [p, cc]
Modified IWG Response and HI	-	× [w]	-	-	-	× [x]	-	× [y]	× [z]	× [p]

Table 4: Table of Events (Continued)

Events Table covers both Phase 1b & 2 (unless otherwise noted)	Screening Period	Treatment Period[a]								Follow-up Period[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		
PB for Pharmacokinetics (AG-120 only in Phase 1b / AG-221 only in Phase 2)	-	× [ee]	-	-	-	× [ee]	-	-	-	-
IP Accountability [dd]	-	×[ff]	-	-	-	×	-	×	×	-
AG-120 / AG-221 Dispensation	-	×	-	-	-	×	-	×		-
Azacitidine Treatment Administration	-	**See Section 7.2 for details**							-	-
Survival Follow-up	-	-	-	-	-	-	-	-	-	× [gg]
Subsequent AML Therapies	-	-	-	-	-	-	-	-	-	× [gg]

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; CR = morphologic complete remission; [redacted] 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; HSCT = hematopoietic stem cell transplantation; ICF = informed consent form; IDH2 = isocitrate dehydrogenase isoform 2; IP = investigational product; IWG = International Working Group; IWRS = interactive web response system; [redacted] MUGA = multi-gated acquisition; PK = pharmacokinetics; PB = peripheral blood; [redacted] SOC = standard of care; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1 family, polypeptide A1

[a] One 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 each treatment cycle 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 enrollment or 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 diagnosis, collecting BMA and PB at screening for potential retrospective confirmation of mutational status, and collecting BMA and PB at screening for pharmacodynamics [redacted].

[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] Source documented only.

[j] The BSA calculation is per the Dubois & Dubois formula: BSA (m^2) = weight (kg)$^{0.425}$ x height (cm)$^{0.725}$/139.2. The dose should be calculated on Day 1 of each treatment cycle. The dose during a treatment cycle should not be amended.

[k] These assessments will be done locally. See Section 6.2 for details.

[l] If an assessment has been performed within 28 days prior to the start of study treatment, it does not need to be repeated.

[m] 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 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.

[n] These assessments will be done centrally. See Section 6.2 for details.

[o] A local serum 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).

[p] Whenever response/diagnosis is assessed in the Follow-up Period (ie, every 8 weeks [± 28 days]). See Section 6.3 for details.

[q] 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.

[r] 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.

[s] Continuous starting after signing ICF through 28 days after the last study treatment. See Section 6.4.1 for details.

[t] 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. Thereafter, transfusions will continue to be collected until the next 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.

[redacted]

[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 progression by a repeated bone marrow assessment at least 1 month later) or required for toxicity assessment. A sample of bone marrow and peripheral blood must also be sent at these time points for central pathology review.

[w] Within 7 days prior to Day 1 of Cycle 2. The assessment is not required at Day 1 of Cycle 1.

[x] Within 7 days prior to Day 1 of Cycle 3. The assessment is not required at Day 1 of Cycle 4.

[y] Within 7 days prior to 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]

[bb] 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.

[cc] A standard cytogenetic metaPhase preparation will be prepared if the bone marrow aspirate is obtained for assessing CR, morphologic relapse, or progressive disease and will be sent to the local laboratory for cytogenetic analysis.

[dd] Including diary cards. See Section 7.6 for details.

[ee] Intensive PK sampling is performed as defined in Table 6 for AG-120 subjects in the Phase 1b Expansion on all subjects, and Table 7 in Phase 2 for AG-221 subjects at select sites for the first 6 - 12 subjects. Sparse PK sampling will be performed on all other AG-221 subjects at the selected sites as well as all other sites as defined in Table 8.

[ff] Cycle 2 only.

[gg] 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 should be collected at the same time schedule. See Section 6.3 for details.

[redacted]

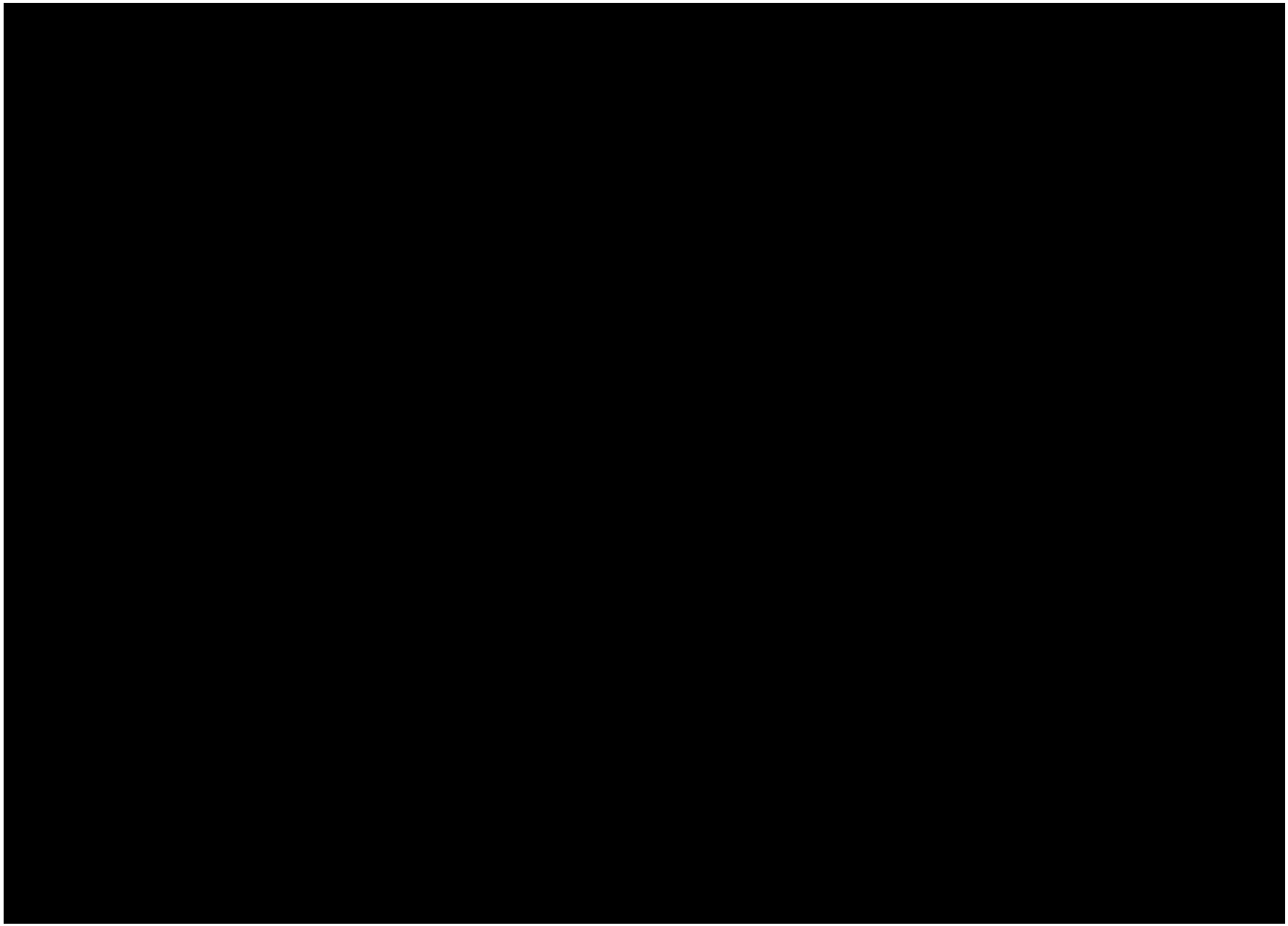


Table 6: AG-120 Intensive Pharmacokinetic Sampling in Phase 1b Expansion

Visit/Cycle:	Cycle 1	Cycle 1	Cycle 2
Study Day:	**D1**	**D15**	**D1**
Pre-dose[a]	X	X	X
Post-dose			
0.5 hr [b]	X	-	X
2 hr [b]	X	-	X
3 hr [b]	X	-	X
4 hr [b]	X	-	X
6 hr [b]	X	-	X
8 hr [b]	X	-	X

[a] Within 30 minutes prior to AG-120
[b] ± 10 minutes
Note: Intensive pharmacokinetic sampling for AG-120 will be conducted during the Phase 1b expansion.

Table 7: AG-221 Intensive Pharmacokinetic Sampling in Phase 2

Visit/Cycle:	Cycle 2	Cycle 3
Study Day:	**D1**	**D1**
Pre-dose[a]	X	X
Post-dose		
2.0 hr[b]	X	-
3.0 hr[b]	X	-
4.0 hr[b]	X	-
6.0 hr[b]	X	-
8.0 hr[b]	X	-
24.0 hr[b]	X	-

[a] Within 30 minutes prior to AG-221
[b] ± 10 minutes
Note: Intensive pharmacokinetic sampling for AG-221 will be conducted at selected sites during Phase 2

Table 8: AG-221 Sparse Pharmacokinetic Sampling in Phase 2

	Cycle 2	Cycle 3
	D1	D1
Pre-dose[a]	X	X
Post-dose		
4.0 hr[a]	X	-

[a] Within 30 minutes prior to AG-221
[b] ± 10 minutes
Note: Sparse pharmacokinetic (PK) sampling for AG-221 will be conducted at all sites during Phase 2. Subjects who participate in the intensive PK will not have additional samples collected.

6. PROCEDURES

Any questions regarding the protocol should be directed to the medical monitor or designee.

Signed 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 period

Screening evaluations 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 once within the screening window, if necessary.

The following will be performed at screening as specified in the Table of Events (Table 4) after written ICF has been signed:

- Registration of screening in interactive web response system IWRS
- Inclusion and exclusion criteria
- Demographics (age, sex, race, and ethnicity)
- Gather information supporting the initial diagnosis of AML by local pathology and cytogenetics, including reports of bone marrow aspirate and/or biopsy, peripheral blood smear, cytogenetics, and other tests if pertinent
- AML diagnosis at screening will be determined by local pathology and cytogenetics review. The pathology will be confirmed retrospectively by a central pathology review. Therefore, bone marrow aspirate (or biopsy if adequate aspirate is not attainable) must be collected at screening such that slides of bone marrow aspirate (and/or biopsy) and peripheral blood smears are available for both the local and the central pathology reviews. 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 standard cytogenetic metaPhase preparation will be prepared from the screening bone marrow aspirate and sent to the local laboratory for cytogenetic analysis.

  The retrospective central pathology review will require a set of duplicate slides for each bone marrow collection time point including bone marrow aspirate (BMA), peripheral blood smear, and bone marrow biopsy (BMB) if performed. The central pathology review will be conducted by personnel blinded to study treatment. The central assessments will be used to confirm AML diagnosis at screening. If the subject was centrally confirmed to not be a candidate for the study, the subject will be replaced for analysis purposes but allowed to remain in the study, and will be excluded from the modified intent-to-treat (mITT) population (Section 9).

  Instructions for submitting slides of bone marrow aspirate (and/or biopsy) and peripheral blood smear for central pathology review are provided in the Study Reference and/or Study Central Laboratory Manual.
- IDH mutational status will be assessed locally; for sites without local testing capabilities, a referral lab will be identified. A bone marrow aspirate and peripheral

blood sample must be sent [redacted] to the central lab for potential retrospective confirmation of mutational status.

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
- Prior procedures including those occurring ≤ 28 days prior to the start of study treatment
- 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
- Body weight
- Height
- 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 or MUGA scan (not required if an assessment 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 clinically significant 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), 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, bilirubin (total and direct), uric acid, lactate dehydrogenase (LDH), AST/SGOT, ALT/SGPT, 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
- At screening, bone marrow aspirate sampling for pharmacodynamic assessments will be performed in subjects of all treatment arms if sufficient bone marrow material remains after bone marrow aspirate sampling for assessing AML diagnosis and testing IDH1 / IDH2 gene mutation status. Refer to the Study Reference and/or Study Laboratory Manual for sample collection, processing, storage, and shipment procedures.

[redacted]

Information to be Collected on Screening Failures

The informed consent date, demographics, and reason the 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).

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. Phase 1b subjects will be enrolled into the appropriate cohort and for Phase 2 IDH2 subjects will be randomized in a 2:1 fashion to receive either oral AG-221 + SC azacitidine or SC azacitidine alone.

Subjects 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. Unless noted otherwise, an administrative window of ± 3 days is permitted for all subsequent visits after the start of study treatment in each treatment cycle 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. Treatment cycles are 28 days in duration, and will occur as described in Section 7.2.

The following evaluations will be performed at the frequency specified in the Table of Events (Table 4) 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 IWRS
- HRQoL outcomes (EORTC QLQ-C30 and EQ-ED-5L questionnaires; see Section 6.8)
- Study drug accountability (where applicable; also refer to Section 7.5)
- Study drug dispensing and administration (where applicable; refer to Section 7)
- 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 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 or MUGA scan if clinically indicated
  - 12-lead ECG. Abnormal finding(s) will be reported on the appropriate eCRF page.
  - For FCBP only, a serum 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 (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 test result 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 T
  - Fasting lipid panel including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides
- Continuous evaluations of AEs, [redacted] concomitant medications and procedures, and transfusions

- Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.
- Bone marrow aspirate (or biopsy if adequate aspirate is not attainable) samples will be collected for assessing response. The site needs to ensure peripheral blood for central hematology is collected and sent at the time of every bone marrow collection. As specified in the Table of Events (Table 4), the frequency is within 7 days prior to study treatment administration on Cycles 2, 3, and 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 progression 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 progression, a standard cytogenetic metaPhase preparation will be prepared and sent to the local laboratory for cytogenetic analysis. 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, and peripheral blood smear collected after the start of study treatment for response assessment must be available for both local and central pathology review. Instructions for submission slides of bone marrow aspirate (and/or biopsy) and peripheral blood smear for central pathology review are provided in the Study Reference and Study Central Laboratory Manuals for sample collection, processing, storage, and shipment procedures.
- Response to treatment, per modified IWG AML response criteria, and HI will be assessed whenever bone marrow samples are collected for response assessment (see immediately above).
- In the Treatment Phase, bone marrow aspirate sampling for pharmacodynamic assessments will be performed only in subjects of the AG-120 (Phase 1b expansion stage only) / AG-221 (Phase 1b dose-finding and 2 randomized stage) treatment arms whenever bone marrow samples are collected for response assessment (see above) and if sufficient bone marrow material remains

[redacted]

- Peripheral blood sampling for PK assessments will be performed for AG-120 during Phase 1b and AG-221 during Phase 2 as detailed in Table 6, Table 7, and Table 8.

- Peripheral blood sampling for pharmacodynamic assessments will be performed in all subjects.

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.

6.2.2. Unscheduled Visits

Should it become necessary to repeat an evaluation (eg, laboratory tests), the results of the repeat evaluation should be entered as appropriate in an additional unscheduled visit page 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 4). 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 IWRS
- HRQoL outcomes (EORTC QLQ-C30 and EQ-ED-5L questionnaires)
- Study drug accountability (where applicable; refer to Section 7.5)
- Study drug dispensing and administration (where applicable; refer to Section 7)
- 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 or MUGA scan 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 markers (not necessary for the EOT Visit if it was last performed within 14 days)
  - Fasting lipid panel (not necessary for the EOT Visit if it was last performed within 28 days)
- Evaluations of AEs, [redacted] concomitant medications, concomitant procedures, and transfusions (monitored through 28 days after the last study treatment)
- Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.
- Bone marrow aspirate and/or biopsy, peripheral blood smear and, if applicable, local cytogenetics, for response assessment (not necessary for the EOT Visit if it was last performed within 28 days)
- Response to treatment, per modified IWG, and HI will be assessed if bone marrow samples are collected for assessing response at the EOT Visit (see above)
- Bone marrow aspirate sampling for pharmacodynamic assessments will be performed in all subjects if bone marrow samples are collected for assessing response at the EOT Visit (see above) and if sufficient bone marrow material remains

[redacted]

- Peripheral blood sampling for pharmacodynamic assessments will be performed in all subjects.

[redacted]

6.3. Follow-up Period

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 Period every 28 days performed by site visits or phone calls:

- AEs, [redacted] concomitant medication, concomitant procedures and transfusions for 28 days after the last study treatment.
  - Thereafter, SAEs made known to the investigator at any time that are suspected of being related to study treatment should be managed as described in Section 10.1.
- Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.
- 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. Information on subsequent AML therapies should be collected at the same schedule as survival follow-up. Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician where allowed by local regulations.
- Females of childbearing potential should avoid becoming pregnant for 4 months after the last study treatment, and male subjects should avoid fathering a child for 4 months after the last study treatment (6 months after the last dose of azacitidine in Canada).

Subjects who discontinue study treatment prior to relapse, progression, or the start of second line therapy will continue to have the following assessments in the Follow-up period every 28 days performed by site visits until confirmation of relapse or progression, or until they have died, or are lost to follow up, or withdrew consent for further data collection, or study closure.

- AEs, [redacted] concomitant medication, concomitant procedures and transfusions for 28 days after the last study treatment.

  - Thereafter, SAEs made known to the investigator at any time that are suspected of being related to study treatment should be managed as described in Section 10.1.

- Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IP administration via use of patient diary or other local procedure in place at the investigational site.
- 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. Information on subsequent AML therapies should be collected at the same schedule as survival follow-up. Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician where allowed by local regulations.
- Females of childbearing potential should avoid becoming pregnant for 4 months after the last study treatment, and male subjects should avoid fathering a child for 4 months after the last study treatment (6 months after the last dose of azacitidine in Canada).
- Bone marrow aspirate and/or biopsy, peripheral blood smear and, if applicable, local cytogenetics report, must be available for local review for assessing response or disease diagnosis, every 8 weeks (± 28 days). In addition, ensure peripheral blood for hematology is collected at the time of every bone marrow collection.
- Response to treatment, per modified IWG, and HI will be assessed if bone marrow samples are collected for assessing response in subjects who discontinue study treatment prior to relapse or progression.

6.4. Safety Assessment

Safety assessments, including physical examination, vital signs, ECG, hematology, serum chemistry, cardiac markers, fasting lipid panel, pregnancy testing (for FCBP subjects only), AEs, concomitant medications and procedures, and transfusions, will be performed at the frequency specified in Table 4: Table of Events, or more frequently if clinically indicated. After screening, ECHO or MUGA scans, urinalysis, and coagulation testing will be performed if clinically indicated.

6.4.1. Adverse Events

Refer to Section 10 for details on AE reporting. Information about common side effects already known about AG-120, AG-221, and azacitidine can be found in the respective IBs or will be communicated between IB. Serious and unexpected events will be communicated in the form of Investigator Notifications. 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 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.

[redacted]

6.5. Efficacy

6.5.1. Response

Bone marrow aspirate (or biopsy if adequate aspirate is not attainable) samples will be collected for assessing response. The site must ensure peripheral blood for central hematology is collected and sent at the time of every bone marrow collection. As specified in the Table of Events, Table 4, the frequency is within 7 days prior to study treatment administration on Cycles 2, 3 and 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 progression as defined in modified IWG AML response criteria (Cheson, 2003) (Appendix F) and International Working Group response criteria in myelodysplasia (Cheson, 2006) 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 progression, a

standard cytogenetic metaPhase preparation will be prepared and sent to the local laboratory for cytogenetic analysis. A bone marrow biopsy can be used for cytogenetics testing if adequate aspirate is not attainable.

Bone marrow aspirate and/or biopsy and peripheral blood smear collected after the start of study treatment must be available for both local and central pathology review. The retrospective central pathology review will require a set of duplicate slides for each bone marrow collection time point including BMA, peripheral blood smear, and BMB if performed. The central pathology review will be conducted by personnel blinded to study treatment.

Response to treatment and HI will be assessed by the investigators according to modified IWG AML Response Criteria (Cheson, 2003) (Appendix F) and IWG myelodysplastic syndromes HI criteria (Cheson, 2006) (Appendix G), respectively.

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

[redacted]

6.5.2. Hematologic Improvement

[redacted]

Hematologic improvement will be assessed through collection of transfusion records and local hematology parameters.

Both response and HI will be assessed locally by the investigators using modified IWG AML response criteria (Cheson, 2003) and IWG response criteria in myelodysplasia (Cheson, 2006), and retrospectively by a blinded Independent Response Adjudication Committee (IRAC) if the study data will be used for regulatory activities.

6.5.3. Survival

Refer to Section 6.3 for survival follow-up.

6.6. Pharmacokinetics

Pharmacokinetic sampling for AG-120 will be conducted on all subjects during Phase 1b AG-120 expansion stage as detailed in Table 6.

During Phase 1b AG-120 expansion stage, subjects enrolled in the AG-120 combination treatment arm will undergo intensive PK assessments, in order to evaluate the PK profile of AG-120 when administered with azacitidine. On Days 1 of Cycle 1 and 2, blood samples will be collected at the following time points: pre-dose (within 30 minutes prior to AG-120) and 0.5 hours (± 10 minutes), 2 hours (± 10 minutes), 3 hours (± 10 minutes), 4 hours (± 10 minutes), 6

hours (± 10 minutes), and 8 hours (± 10 minutes) post-dose. Pre-dose blood samples (trough) will also be obtained on C1D15.

During Phase 2 AG-221 randomization stage, the first twelve subjects at selected sites in the AG-221 combination treatment arm will undergo intensive PK assessments (Table 7) over a 24-hour period on C2D1 to C2D2, in order to evaluate the PK profile of AG-221 when administered with azacitidine. Blood samples will be collected at the following time points: pre-dose (within 30 minutes prior to AG-221) and 2 hours (± 10 minutes), 3 hours (± 10 minutes), 4 hours (± 10 minutes), 6 hours (± 10 minutes), 8 hours (± 10 minutes,) and 24 hours (± 10 minutes) post-dose. Pre-dose blood samples (trough) will also be obtained on C3D1.

The subjects not being assessed for intensive PK in the AG-221 treatment arm during the Phase 2 segments will undergo sparse PK samples for measurement of AG-221 concentration (Table 8). Blood samples will be collected at pre-dose (within 30 minutes prior to dosing) and 4 hours (± 10 minutes) post-dose on Day 1 of Cycle 2, and pre-dose on Day 1 of Cycle 3.

No PK samples will be collected from subjects who are randomized to the azacitidine alone treatment arm.

The peripheral blood sample should be collected by an in-dwelling catheter or by venipuncture into sample collection tubes. Sample collection kits and supplies will be provided by the sponsor or sponsor-designated vendor. Blood samples for sparse PK should be processed promptly and plasma harvested and stored according to the instructions in the Study Reference and/or Study Laboratory Manual.

6.7. Pharmacodynamics, [redacted]

Bone marrow, blood [redacted] samples for biomarker assessments (pharmacodynamics, [redacted]) should be collected according to the Table of Events, in parallel with collection of bone marrow for disease assessment time points. Sample collection, processing, storage, and shipment procedures will be provided in the Study Reference and/or Study Central Laboratory Manual.

Bone marrow and blood will be collected at baseline and during the course of treatment for correlative analyses to provide information on drug mechanisms of action relevant to clinical response. Pharmacodynamic measurements will include assessment of [redacted] 2-HG levels in blood and/or bone marrow. [redacted] Results from these studies will be evaluated in association with parameters of clinical benefit, to determine if biomarkers of response or non-response to treatment may be identified.

[redacted]

6.8. 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-5L, will be used for evaluating HRQoL outcomes.

The EORTC QLQ-C30 (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 N for an example.

The EQ-5D-5L 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-5L is available in many languages and it takes approximately 5 minutes to complete. EQ-5D-5L data will be captured using a portable electronic tablet computer. See Appendix O for an example.

It is important that every subject completes all assessments of EORTC QLQ-C30 and EQ-5D-5L at every specified time point, prior to dosing and prior to interaction with study personnel, to minimize missing data and subject bias.

[redacted]

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

7.1.1. AG-120

Celgene Corporation will supply AG-120, 250 mg strength tablets. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products.

AG-120 tablets will be packaged in an appropriate container with child resistant closures and will be labeled appropriately as IP for this study.

Packaging and labeling will be prepared to meet all regulatory requirements.

Bottles of AG-120 tablets must be stored according to the package label. All investigational products must be stored in a secure, limited-access location and may be dispensed only by the investigator or by a member of the staff specifically authorized by the investigator.

7.1.2. AG-221

Celgene Corporation will supply AG-221, 50-, 100-, 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.

AG-221 tablets will be packaged in an appropriate container with child resistant closures and will be labeled appropriately as IP for this study.

Packaging and labeling will be prepared to meet all regulatory requirements.

Bottles of AG-221 tablets must be stored according to the package label. All investigational products must be stored in a secure, limited-access location and may be dispensed only by the investigator or by a member of the staff specifically authorized by the investigator.

7.1.3. 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.

For subcutaneous administration, vials containing 100 mg of freeze-dried azacitidine will be reconstituted with 4 mL sterile water for injection. Azacitidine degrades rapidly at room temperature following reconstitution; therefore, the azacitidine suspension should be prepared immediately before use and the reconstituted suspension should be administered within 45 minutes. If elapsed time is greater than 45 minutes, the reconstituted suspension should be discarded appropriately and a new dose prepared. Alternatively, if the product needs to be reconstituted in advance of administration, it must be placed in a refrigerator (2°C to 8°C [36°F to 46°F]) immediately after reconstitution, and kept in the refrigerator for a maximum of 8 hours. If the elapsed time in the refrigerator is greater than 8 hours, the suspension should be discarded appropriately and a new dose prepared. 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 (70°F to 77°F). If the elapsed time is longer than 30 minutes, the suspension should be discarded appropriately and a new dose prepared.

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

Azacitidine will be packaged and labeled appropriately as IP and will meet all regulatory requirements.

7.2. Treatment Administration and Schedule

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 have been 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.

The first day of study treatment dosing is considered Day 1 of a cycle.

Subjects will be monitored for hematologic toxicity and non-hematologic toxicity with the 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 treatment response during study treatment.

Overdose, as defined for this protocol, refers to AG-120, AG-221, and azacitidine dosing.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of AG-120, AG-221, and azacitidine assigned to a given subject, regardless of any associated adverse events or sequelae.

PO any amount 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 case report form. See Section 10 for the reporting of adverse events associated with overdose.

Subjects can continue to receive study treatment provided that they benefit from study treatment and have an acceptable toxicity profile. Study treatment can 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. Treatment Administration

7.2.1.1. Dispensation and Administration of AG-120 or AG-221

Phase 1b Dose-finding and AG-120 Expansion Stage

AG-120 given at 500 mg in cohort 1 or 250 mg in cohort -1, orally QD on Days 1 – 28 of each 28-day cycle until treatment discontinuation (Section 11.1).

AG-221 is given at 100 mg in cohort 1, 200 mg in cohort 2, or 50 mg in cohort -1, orally QD on Days 1 – 28 of each 28-day cycle until treatment discontinuation (Section 11.1).

Phase 2 AG-221 Randomization Stage

AG-221 is given at the RCD orally QD on Days 1 – 28 of each 28-day cycle until treatment discontinuation (Section 11.1).

Phase 1b (Dose-finding and AG-120 Expansion) and Phase 2 AG-221 Radomomized Stage

AG-120 or AG-221 will be dispensed on Day 1 of each treatment cycle, with sufficient IP to complete a 28-day cycle. Subjects should be instructed to open AG-120 or AG-221 packaging as close as possible to when they are going to take AG-120 or AG-221, inspect each AG-120 or 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 ± 6 hours. 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. Fasting is required for 2 hours prior to and 1 hour following AG-221 administration. Water is allowed during fasting. Fasting is not required for AG-120 administration.

All efforts should be made to administer AG-120 or 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 be documented in the subject diary and not be taken beyond the last scheduled day of AG-120 or AG-221 administration, but should be returned by the subject for drug accountability.

If vomiting occurs shortly after a dose of AG-120 or AG-221 administrated, that dose should not be made up later that 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 and document this in the subject diary.

In order to optimally benefit from the treatment, investigators should aim to treat patients for at least 6 cycles, although patients can be discontinued from protocol earlier if they demonstrate unacceptable toxicity or relapse after CR or PR, transformation to AML, or disease progression.

7.2.1.2. Dispensation and Administration of Azacitidine

SC azacitidine will be prepared as detailed in Appendix H.

Subjects randomized to the azacitidine arm will receive azacitidine 75 mg/m^2/day SC for 7 days every 28 days until treatment discontinuation (Section 11.1). In addition, subjects may receive

BSC as needed (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 best supportive care; see current version of Prescribing Information), including antibiotics and transfusions, per investigator discretion. In the event 2 or fewer doses are missed during the 7-day dosing period, dosing should continue so the subject receives the full 7 days of therapy. If 3 or more days are missed during the 7-day dosing period, the investigator should contact the sponsor and a decision on dosing will be made on a case-by-case basis.

In order to optimally benefit from the treatment, investigators should aim to treat patients for at least 6 cycles, although patients can be discontinued from protocol earlier if they demonstrate unacceptable toxicity or relapse after CR or PR, transformation to AML, or disease progression.

7.2.2. Treatment Schedule

7.2.2.1. Phase 1b Dose-finding Stage

The dose finding will use a "3 + 3" design. During the dose-finding phase, consented eligible subjects will be enrolled into one cohort of AG-120 or sequential cohorts of increasing doses of AG-221.

7.2.2.1.1. AG-120 Cohorts

The dosing cohorts for subjects with an IDH1 gene mutation treated with AG-120 will be as follows:

Table 9: AG-120 Cohorts

	IDH1 mutant
Cohort	**AG-120 dose**
Cohort -1	250 mg QD
Cohort 1	500 mg QD

7.2.2.1.2. AG-120 Expansion Stage

Phase 1b dosing of the AG-120 expansion cohort will be the RCD, as declared by the DRT, based on AG-120 + SC azacitidine data.

7.2.2.1.3. AG-221 Cohorts

The dosing cohorts for subjects with IDH2 gene mutation treated with AG-221 will be as follows:

Table 10: AG-221 Cohorts

	IDH2 mutant
Cohort	**AG-221dose**
Cohort -1	50 mg QD
Cohort 1	100 mg QD

Table 10: AG-221 Cohorts (Continued)

Cohort	IDH2 mutant AG-221dose
Cohort 2	200 mg QD

7.2.2.1.4. Azacitidine

The dosing for azacitidine will be 75 mg/m^2/day SC for 7 days of each 28-day cycle for all cohorts in both IDH1 and IDH2 gene mutation subjects.

7.2.2.2. Phase 2 AG-221 Randomization Stage

Randomization occurs via IWRS after confirming ongoing eligibility of the subject. All subjects randomized will be stratified by primary (ie, de novo) or secondary (progression of MDS or myeloproliferative neoplasms [MPN], or therapy-related) AML according to the WHO classification (Appendix B).

Oral AG-221 + SC azacitidine treatment arm will be initiated at the RCD of AG-221 on Days 1 - 28 of each 28-day treatment cycle. Both combination and single agent azacitidine will be administered at 75 mg/m^2/day SC for 7 days of each 28-day cycle. Pending the outcome of the Phase 1b dose-finding, a dose escalation of AG-221 to 200 mg daily may be initiated to augment treatment response as stated in Section 7.2.2.3.1 below.

[redacted]

7.2.2.3.1. Dose Modifications for AG-120 or AG-221

Dose modification due to toxicities

If a certain level of toxicity (eg, Section 7.2.2.3.2) is observed after initiation of AG-120 or AG-221 treatment and is considered as possibly or probably related to treatment, dosing could be interrupted or delayed. Upon resolution of the toxicity, dosing may be resumed with a one-level dose reduction at the discretion of the investigator. Any subject who is unable to tolerate 250 mg QD of AG-120 or 50 mg QD of AG-221 should be discontinued from study treatment.

Refer to Table 11 for sequential dose levels.

If treatment is modified during the course of the study and benefit is demonstrated after a reduced dose level, that dose level should be maintained during subsequent treatment cycles unless toxicity develops.

Table 11: AG-120 and AG-221 Hematologic and Non-hematologic Toxicity Dose Levels

Dose Level	IDH1	IDH2
	AG-120	AG-221
-1	250 mg QD	50 mg QD
1	500 mg QD	100 mg QD
2	NA	200 mg QD

Dose escalation for augmenting treatment responses

If during the Phase 1b segment of this study the 200 mg dose is confirmed by the DRT as safe, the AG-221 dose may be escalated for the subsequent treatment cycles from 100 mg QD to 200 mg QD if the following occurs:

- no partial remission (PR) is achieved after treatment with AG-221 for at least 2 cycles without ≥ Grade 3 AEs suspected by the investigator to be related to AG-221; or
- no complete remission (CR) is achieved after treatment with AG-221 for at least 4 cycles without ≥ Grade 3 AEs suspected by the investigator to be related to AG-221; or
- evidence of morphologic relapse or progression of disease.

If benefit is demonstrated at 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 (see Section 7.2.2.3.2) is observed and is considered as possibly or probably related to AG-221 treatment. Only one dose escalation will be allowed, and the AG-221 dose cannot be re-escalated more than once.

7.2.2.3.2. Toxicities During AG-120 or AG-221 Treatment

Hematologic toxicities

Hematologic toxicities of cytopenias (> 50% decrease from baseline [Day 1 of Cycle 1]) and/or marrow cellularity < 5% on Day 28 of a cycle or later without evidence of leukemia.

Prolonged hematologic toxicities during study treatment should result in a discussion between the investigator and the medical monitor.

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

The discussion of the emergency management of torsade de pointes and its hemodynamic consequences is beyond the scope of this guideline.

[redacted] As of 01 May 2015, 6 (10.5%) of 57 subjects in Study AG120 C 001 have experienced QT prolongation while receiving AG 120. QTc interval has been observed in dogs at relatively low doses of AG-221. Prolonged QTc interval has not been seen in other animal species at high doses.

Subjects may be at increased risk for the development of QT prolongation when treated with AG 120 administered with fluoroquinolones, azole antifungal agents, or serotonin (5-HT3) antagonists. Investigators need to be vigilant; refrain from administering concomitant medications associated with QT prolongation, and if no other therapeutic options are available, monitor subjects receiving AG-120 with the combination of these drugs, and evaluate ECG and electrolytes (including potassium, magnesium, and calcium) particularly in subjects presenting with nausea, vomiting, or diarrhea.

Please refer to the AG-120 Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of AG-120.

Subjects who experience prolongation of the heart-rate corrected QT interval, Fridericia's correction (QTcF) to > 480 msec (Grade ≥ 2) while treated with AG-120 or 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), investigational product 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, re-challenge with AG-120 or 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-120 or AG-221 may be reduced to a dose approved by the medical monitor without interruption of dosing. The AG-120 or AG-221 dose may be re-escalated to the prior dose in ≥ 14 days after QT prolongation has decreased to ≤ Grade 1.
  - If Grade 3 (QTcF > 500 msec), when QTc prolongation is first observed, hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. Dosing with AG-120 or AG-221 will be interrupted. If QTc returns to within 30 ms of baseline or < 450 msec within 14 days, treatment may be resumed at a reduced dose. The AG-120 or 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 hospital when QTc prolongation is first observed for continuous cardiac monitoring and be discharged only after review by a cardiologist. Dosing with AG-120 or AG-221 should be permanently discontinued.

IDH Differentiation Syndrome

Subjects treated with AG-120 or AG-221 may develop signs and symptoms of a IDH Differentiation Syndrome. Signs and symptoms could include fever, dyspnea, edema/ weight gain, increased serum creatinine and, in some cases, clinical features consistent with the acute respiratory distress syndrome with associated pulmonary infiltrates, and pulmonary or pericardial effusions. Increases in white blood cell (WBC) count concurrent to Differentiation Syndrome has been observed, but by itself do not substantiate the syndrome. No single sign or symptom may be considered per se as diagnostic of the syndrome.

Corticosteroids should be promptly initiated at a suggested dose 10 mg of dexamethasone IV every 12 hours until resolution of IDH Differentiation Syndrome, after which the dose can be progressively reduced in the next few days or weeks.

Further information on diagnosis and treatment of IDH Differentiation Syndrome can be found in the supplemental guidance document.

Leukocytosis

Initiation of treatment with the differentiating agents may lead to rapid WBC expansion not associated with infectios process and not manifesting with the signs and symptoms of IDH Differentiation Syndrome discussed above.

In subjects with elevated WBC, prompt initiation of hydroxyurea is suggested, as per standard local practices (eg, dose of 2 to 3 g PO twice or three times daily for WBC > 30 x 10^9/L). In case of severe leukocytosis (WBC >100 x 10^9/L), use of leukapheresis may be appropriate. Subject should be regularly monitored for changes in WBC count and for new signs and symptoms of infection or IDH Differentiation Syndrome.

Gastrointestinal Disorders

Appropriate monitoring and timely management of gastrointestinal toxicities, as appropriate, is critical in avoiding malnourishment and dehydration.

Abnormal Level of Liver Enzymes

Subjects with elevations in ALT ≥ 3-fold ULN, subjects will be monitored using the algorithm:

- Repeat LFT (ie, ALT, AST, total bilirubin, ALP, GGT) within < 3 days of the initial test. FU 2-3 times weekly, and weekly when stable
- Perform additional diagnostic follow up:

- Focused medical history, including review of prior history of liver or biliary disorders, concurrent symptoms, review of all concomitant medications [eg, acetaminophen-containing medications, over-the-counter or herbal medications, nutritional supplements] including any changes in medications, detailed review of alcohol use
- Hepatitis serology (anti-HAV, HBsAg, anti-HBs, anti-HB core, anti- HCV, HCV RNA, EBV and CMV screen), and autoantibodies (eg, ANA, anti-smooth muscle antibody)
- Complete physical examination
- Liver ultrasound and follow-up imaging as appropriate
- Additional evaluation as appropriate (INR, PT)

7.2.2.3.3. Initiation of Each AG-120 or AG-221 Treatment Cycle

In order to proceed to the next AG-120 or AG-221 treatment cycle, subjects must continue to meet entry level values regarding renal and hepatic function (see Section 4.2).

In addition, hematologic 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]). If the subject does not meet these criteria, the start of the next cycle will be delayed. If the hematologic toxicity is attributed solely to the administration of azacitidine, AG-120 or AG-221 may continue to be given daily until recovery of counts as described below in Section 7.2.2.3.4. The initiation of a new cycle will start upon the ability to reinitiate the combination therapy. If there is a delay of more than 28 days (4 weeks) in the start of the next treatment cycle, the medical monitor should be consulted for the risks and benefits of continuing AG-120 or AG-221 or combination treatment. Subjects who experience persistent Grade ≥ 3 toxicity that are assessed as possibly or probably related to AG-120 or AG-221 treatment may continue AG-120 or AG-221 treatment if, in the opinion of the investigator and the medical monitor, the subject is experiencing clinical benefit from AG-120 or AG-221 treatment.

The initiation of a new cycles will start upon the administration of the 7 day of SC azacitidine.

7.2.2.3.4. Dose Modifications Guidelines for Azacitidine

The first treatment cycle of azacitidine should always be given at 100% of the dose, 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 by the guidance below. Azacitidine dose level modifications should be made taking the subjects clinical situation including previous adverse events (e.g. bleeding or infections) and the status of the subjects disease into account. If the dose of azacitidine is modified during the course of the study (see below) and benefit is demonstrated at the reduced dose, that dose should be maintained during subsequent cycles (unless toxicity develops). The investigator should contact the medical monitor for guidance on azacitidine dose modification, if needed.

Cycle length is 28 days unless a delay for toxicity/AE is encountered. Generally, the initiation of a new cycle will be defined as Day 1 of the azacitidine administration or Day 29 of the AG120/AG221 administration in case azacitidine has been permanently discontinued.

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 (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.

Necrotising fasciitis, including fatal cases, have been reported in patients treated with azacitidine. Azacitidine therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

If azacitidine is permanently discontinued in the combination arms, AG-120 or AG-221 may continue at the discretion of the investigator.

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 4: Table of Events, and as needed to monitor 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, white blood count [WBC] ≥ 3.0 x 10^9/L, ANC ≥ 1.5 x 10^9/L, and platelets ≥ 75.0 x 10^9/L) prior to 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 absolute neutrophil count 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 I.

Table 12: Hematologic Dose Reductions Based on ANC and Platelets

Nadir Counts		% Dose in the next course if recovery[a] is not achieved in next 14 days
ANC (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 treatment

Following azacitidine treatment, if the decrease in WBCs 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:

Table 13: Hematologic Dose Reductions based on Bone Marrow Cellularity

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 J.

Renal Dysfunction During Azacitidine Therapy

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported rarely in subjects treated with intravenous azacitidine administered 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).

For subjects in the AG-120 and AG-221 combination arms, AG-120 and AG-221 can continue to be taken if azacitidine is interrupted beyond the 28 day cycle as long as the daily AG-120 and AG-221 are not felt to have been part of the reason for interruption.

7.3. Method of Treatment Assignment

In the dose-finding phase, each dose cohort will initially enroll 3 subjects. The dose of AG-120 and AG-221for each subject will be based on the assigned cohort. Azacitidine will be administered at 75 mg/m^2/day SC for 7 days of each 28-day cycle across all cohorts.

Once the RCD is determined , enrollment will begin in Phase 1 expansion for IDH1 subjects or in Phase 2 of the study for IDH2 subjects. As noted in Section 3.1.2, subjects with IDH2 mutation will be randomized to receive oral AG-221 + SC azacitidine (Arm 1) versus SC azacitidine (Arm 2) in a 2:1 ratio. Arms 1 will randomize a minimum of 66 subjects and 2 will randomize a minimum of 33 subjects (99 subjects total in both arms).

Subjects in the Phase 2 segment will be stratified by primary (ie, de novo) or secondary (progression of MDS or myeloproliferative neoplasms [MPN], or therapy-related) AML according to the WHO classification (Appendix B).

An IWRS will be used to track subject enrollment / randomization to the treatment arms and dosing. Assignment of drug kit will be performed by contacting IWRS at Day 1 of each cycle.

Celgene trial staff will review and verify documented specific eligibility criteria for all screened subjects prior to allowing enrollment of subjects via the IWRS but enrollment / randomization is ultimately the responsibility of the investigator.

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

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

Investigational product returned and issued to 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 non-investigational product (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 investigational product 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) 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 return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

If drug 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 to Celgene. Any revisions to a site's destruction process must be provided, approved, and documented 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.

Site staff will administer 7 doses of azacitidine. On the days of PK assessments subjects will be instructed not to take AG-120 or AG-221, as AG-120 or AG-221 will be administered by the site. All other days subjects self administer AG-120 or AG-221 at home. Documentation of AG-120 or AG-221 dosing during treatment will be recorded in a study specific diary card. AG-120 or AG-221 administration diary cards will be provided by the sponsor to study site personnel, who will in turn distribute them to study subjects randomized to receive AG-120 or AG-221 treatment. Study site personnel will enter the scheduled daily doses, the number of tablets to be taken each day and any other applicable information. Study site personnel will review the dosing information with the subject (or legally authorized representative). Subjects (or legally authorized representative) will be asked to record AG-120 or 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. Diary cards must be saved and kept with the source documentation. Study site personnel will perform a AG-120 or AG-221 administration compliance check and record this information in the subject's source documentation and on the appropriate eCRF page.

Accurate recording of study treatment administration (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

8.1. Concomitant Therapy Known to Prolong QT Interval Requiring Careful Monitoring

Concomitant use of drugs with a potential to prolong the QT interval should be avoided and these drugs should be replaced with alternative treatments if possible. If this is not possible, subjects receiving these drugs should be adequately monitored by EKG controls, drug concentrations (where applicable), and serum electrolytes like potassium and magnesium.

These medications include but are not limited to:

- Fluoroquinolones such as ciprofloxacin and moxifloxacin
- Azole antifungals such as fluconazole and posaconazole
- Serotonin (5-HT_3) antagonists such as granisetron and ondansetron

Other examples of drugs known to prolong the QT interval are listed in (Appendix M).

8.2. Drug-Drug Interactions

AG-120 is a direct inhibitor of CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 and is a potential inducer of CYP2B6 and CYP3A4. AG-221 is a direct inhibitor of CYP2C8, CYP2C9, CYP2C19, and CYP2D6 and is an inducer of CYP3A4. Subjects should not use sensitive substrates of these CYP isoforms during treatment with AG-120 or AG-221.

Subjects taking sensitive CYP2B6 or 2C9 and other substrate medications listed in Appendix K may require dosage adjustment or transfer to other similar medications that are not sensitive to metabolism through these pathways prior to enrolling. Subjects taking medications with narrow therapeutic windows listed in Appendix K, should be excluded or monitored appropriately, unless they can be transferred to other medications prior to enrolling.

AG-120 is a substrate for P-glycoprotein (P-gp), but not BCRP. In addition, AG-120 is an inhibitor of P-gp and a weak inhibitor of BCRP. AG-221 is not a substrate of either BCRP or P-gp, but is a strong inhibitor of both. Subjects should not use sensitive P-gp or BCRP substrates during treatment with AG-120 or AG-221, nor potent P-gp inhibitors during treatment with AG-120, unless the medications can be properly monitored during the study (Appendix L).

As AG-221 is an inhibitor of UGT1A1, the metabolism of drugs that are substrates for UGT1A1, including ezetimibe, raloxifene and raltegravir, may be slowed, leading to increased exposure to these compounds. Therefore, subjects on these drugs should be monitored for adverse events associated with the respective products and for elevations in indirect bilirubin levels, and should be switched to lower doses or alternate therapies, if necessary.

8.3. Permitted Concomitant Medications and Procedures

Medications and treatments other than those specified above are permitted during the study. All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the investigator according to acceptable local standards of medical care. Subjects should receive analgesics, antiemetics, anti-infectives (with the exception of macrolide

antibiotics, anti-retroviral medications, and rifampin), antipyretics, and blood products as necessary.

Growth factors (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]) can be used to support subjects who have developed dose-limiting Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection. The use of erythropoiesis stimulating agents is permitted according to the American Society of Clinical Oncology Guidelines (Rizzo, 2010).

COVID-19 vaccines that are NOT live can be administered while the subject is receiving the study drug treatment and after the last administration of study drug. COVID-19 vaccines that are NOT live should be handled in the same manner as other vaccines. The following are NOT considered live vaccines and the decision to vaccinate should be made by the investigator and participant: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines, toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (eg, Pfizer/BioNTech and Moderna COVID-19 vaccines) and replication-incompetent recombinant vector vaccines.

If a subject has received a specific COVID-19 vaccination during the course of the study, the type of vaccine and date(s) received should be recorded on the concomitant medications eCRF page.

No data are available on the response to COVID-19 vaccines. The efficacy and safety of the vaccination in subjects who are receiving AG221 or AG120 or azacitidine are unknown. Please contact the Medical Monitor with any questions related to COVID-19 vaccines.

8.4. Prohibited Concomitant Medications and Procedures

No new investigational treatment shall be initiated while the subject is participating in the Treatment Phase of this clinical trial.

Live COVID-19 vaccines should generally not be administered to a subject during the study, including the treatment period, safety follow-up period [redacted]. Live vaccines are defined as those that are capable of transmitting infectious SARS-CoV-2 or other viruses. If it cannot be determined whether or not the vaccine is live, it is recommended that the vaccine not be administered until it is confirmed that there is no risk of viral infectivity within the subject.

No data are available on the response to COVID-19 vaccines. The efficacy and safety of the vaccination in subjects who are receiving AG120 or AG221 or azacitidine are unknown. Please contact the Medical Monitor with any questions related to COVID-19 vaccines.

[redacted]

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 a Phase 1b/2, multicenter, randomized, study to evaluate the safety and efficacy of oral AG-120 or AG-221 administered with subcutaneous azacitidine versus azacitidine alone in subjects with newly diagnosed acute myeloid leukemia (AML) with an IDH1 or IDH2 mutation. The Phase 1b Stage will be an open-label, combination dose-finding and dose expansion study that will evaluate the safety and clinical activity of oral AG-120 or AG-221 administered with subcutaneous azacitidine in subjects with newly diagnosed AML with an IDH1 or IDH2 mutation. The Phase 2 AG-221 Randomized Stage of the study will be an open label randomized 2-arm design to evaluate the efficacy and safety of oral AG-221 administered with SC azacitidine versus azacitidine alone in subjects with newly diagnosed AML who are not candidates to receive intensive IC and have IDH2 mutations. Phase 1b segment will determine the recommended combination dose (RCD) of AG-120 and AG-221 with azacitidine separately. RCD of AG-120 administered with azacitidine will be used in the Phase 1b AG-120 expansion stage RCD of AG-221 administered with azacitidine will be used in Phase 2 AG-221 randomized stage of the study.

All data will be summarized by study stage. In the analysis of the Phase 1b data, the results will be presented by dose cohort. In the analysis of the Phase 2 data, the results will be presented by 2 arms: AG-221 + azacitidine and azacitidine mono therapy. The statistical comparisons will be conducted for AG-221 + azacitidine versus azacitidine mono therapy. In addition, where appropriate, a total column will be included to summarize subjects across cohorts/treatment groups. Summaries of continuous variables will present the number of subjects included in the analysis (N), the mean and standard deviation (SDev) , the median, the minimum and the maximum values. 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 cohort/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

The following analysis sets will be evaluated and used for presentation of the data in Phase 1b and Phase 2 stages.

9.2.1. Phase 1b Dose-finding Stage

Full Analysis Population

Full analysis population (FAP) includes all subjects who were enrolled and received at least 1 dose of study treatment. Subjects will be classified according to the assigned dose level and

schedule. FAP is the primary analysis population and will be the default analysis set for all analyses except the safety analyses, unless otherwise specified.

DLT-Evaluable Population (DEP)

Dose Determining Set (DDS): Subjects who take at least one dose of study drug in Phase 1b dose-finding stage and either have a DLT during Cycle 1 regardless of amount of study drug exposure, or have no DLT and complete at least 75% of AG-120 or AG-221 doses (21 out of 28 days) and a minimum of 5 doses of azacitidine, and at least 50% of the planned combination doses for AG-120 or AG-221 and azacitidine administered together (in the same day for 4 out of 7 days) in the first 28 days from Cycle 1 Day 1 and are also considered by the Clinical Study Team to have sufficient safety data available to conclude that a DLT does not occur during Cycle 1. A subject diary will be used during outpatient treatment to record details around AG-120 and AG-221 dosing. Subjects in this population set will be denoted as evaluable for DLT assessment and RCD estimation.

Safety Population

Safety population includes all subjects who were enrolled and received at least one dose of study treatment. Subjects will be classified according to the treatment received, where treatment received is defined as the assigned dose level/schedule if it was received at least once, or the first dose level/schedule received if assigned treatment was never received. The safety population will be the primary set for the analysis of safety data.

Evaluable Analysis Population

Evaluable Analysis Population (EAP) includes all subjects in the FAP for whom the baseline response assessment and at least one post baseline response assessment at Day 28 or later are available and evaluable. The clinical activity of AG-221/AG-120 combined with azacitidine will be primarily assessed in the FAP. Additional efficacy analyses may be conducted for the EAP.

9.2.2. Phase 1b AG-120 Expansion Stage

Full Analysis Population

Full analysis population (FAP) includes all subjects who were enrolled and received at least 1 dose of study treatment. Subjects will be classified according to the assigned dose level and schedule. FAP is the primary analysis population and will be the default analysis set for all analyses except the safety analyses, unless otherwise specified.

Safety Population

Safety population includes all subjects who were enrolled and received at least one dose of study treatment. Subjects will be classified according to the treatment received, where treatment received is defined as the assigned dose level/schedule if it was received at least once, or the first dose level/schedule received if assigned treatment was never received. The safety population will be the primary set for the analysis of safety data.

Evaluable Analysis Population

Evaluable Analysis Population (EAP) includes all subjects in the FAP for whom the baseline response assessment and at least one post baseline response assessment at Day 28 or later are

available and evaluable. The clinical activity of AG-221/AG-120 combined with azacitidine will be primarily assessed in the FAP. Additional efficacy analyses may be conducted for the EAP.

9.2.3. Phase 2 AG-221 Randomization Stage

Intent-to-Treat Population

The ITT population includes all subjects who are randomized to treatment, regardless of whether they received treatment or not. The ITT population is the primary analysis population for Phase 2 segment.

Modified Intent-to-Treat Population

The mITT population includes all subjects who have met all inclusion and exclusion criteria and experienced no major protocol deviations during the study, received at least one dose of study treatment, and had at least one response assessment performed.

Safety Population

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

Evaluable Analysis Population

Evaluable Analysis Population (EAP) includes all subjects in the ITT for whom the baseline response assessment and at least one post baseline response assessment at Day 28 or later are available and evaluable. The clinical activity of AG-221 combined with azacitidine will be primarily assessed in the ITT. Additional efficacy analyses may be conducted for the EAP.

Pharmacokinetics Population

The PK population includes all subjects who enroll and receive at least one dose of study drug (AG-221/AG-120) and have at least 1 measurable concentration datum of study drug.

9.3. Sample Size and Power Considerations

The Phase 1b dose-finding stages will enroll a total of approximately 24 subjects. Additional subjects may be enrolled in a dose level to replace subjects who are not evaluable for the primary endpoint, or for further exploring safety, PK, PK/pharmacodynamic, or preliminary clinical activity.

In Phase 1b AG-120 expansion stage, to ensure acceptable toxicity at the RCD, up to 15 subjects will be accrued into the AG-120 expansion phase. Based on a sample size of 18 AML subjects treated at RCD (ie, 15 subjects in the dose expansion and around 3 subjects in the dose escalation), there is 95% probability of detecting 1 or more AEs with an underlying rate of 15%, and 85% probability of detecting 1 or more AEs with an underlying rate of 10%.

In Phase 2 AG-221 randomized stage, subjects with AML with IDH2 mutation will be randomized to receive oral AG-221 + SC azacitidine versus SC azacitidine in a 2:1 ratio. A minimum of 99 subjects will be randomized in this phase with 66 subjects in the oral AG-221 + SC azacitidine arm, and 33 subjects in the SC azacitidine mono therapy arm. The statistical comparisons will be conducted for oral AG-221 + SC azacitidine versus azacitidine mono

therapy. Assuming an overall response rate (ORR) of 30% in the azacitidine mono therapy and an ORR of 50% for oral AG-221+ SC azacitidine arm, the sample size of 66 subjects in AG-221 + SC azacitidine arm and 33 patients in SC azacitidine mono therapy arm will provide 75% power to detect an 20% difference in ORR at a two-sided type I error rate of 0.2. The multiple comparison was not considered in the sample size calculation.

[redacted]

9.4. Background and Demographic Characteristics

Demographic and baseline disease characteristics will be summarized by study phase and by cohort/treatment group within the Phase 1b and Phase 2 segments. Age, height, body weight, and other 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 summarized using frequency tabulations (count, percentage).

9.5. Subject Disposition

Subject disposition (analysis population allocation, subjects who entered, discontinued treatment/study, along with primary reason for discontinuation) will be summarized using frequency and percentage for study phase/follow-up periods and by cohort/treatment arm. A summary of enrolled subjects by study phase, by site, and by country will be provided as well. Protocol deviations/violations will be summarized using frequency tabulations. Supportive corresponding subject listings will also be provided.

9.6. Efficacy Analysis

9.6.1. Phase 1b

Response to treatment will be confirmed internally using modified IWG.

Subjects who discontinue study treatment to receive HSCT will remain on study and will be followed until documented disease progression or end of trial.

Point estimates and 95% confidence intervals for response rates will be summarized for each dose level and overall. Response will be summarized as investigator-assessed overall response rate (ORR), which includes responses of CR, CRp, CRi, morphologic leukemia-free state (MLFS), and PR. Other measures of clinical activity, including duration of remission, duration of response, EFS, Sponsor-assessed CR/ CRh (based on laboratory dataset), overall survival, and time to remission/response may be summarized as appropriate. All time to event endpoints will be estimated using Kaplan-Meier methods. Point estimates and 95% confidence intervals will be provided where appropriate.

9.6.2. Phase 2 AG-221 Randomized Stage

For subjects in Phase 2, response will be primarily assessed by investigator review.

All efficacy analysis will be performed in the ITT population. Key efficacy analysis will also be performed on the mITT and EAP as supportive evidence and to assess the robustness of the efficacy findings. Subjects will be analyzed according to randomized treatment group.

The primary efficacy endpoint ORR is defined as the rate of responses including CR, CRi, CRp, MLFS and PR that are assessed by investigator according to modified IWG AML response criteria. The ORR will be summarized by treatment group. The treatment difference in ORR will be tested using the Chi squared test at a two-side 0.2 level and in the ITT population. This test will provide the pivotal p-value for the comparison of the ORR of the oral AG-221 + SC azacitidine versus azacitidine mono therapy. Estimated response rate with 80% and 95% confidence intervals will also be provided.

Event-free survival (EFS) is defined as the interval from the date of randomization to the date of documented morphologic relapse, progression, or death from any cause, whichever occurs first. The analysis of the **EFS** will be conducted using the log-rank test in the ITT population. This test will be used for the comparison of the two EFS curves of oral AG-221+ SC azacitidine versus azacitidine mono therapy. The Cox proportional hazards regression model will be used to estimate the hazard ratio and a 95% confidence interval for the hazard ratio.

Duration of response is defined as time from the first documented CR/CRi/CRp/MLFS/PR to the date of the first documented morphologic relapse, progression according to modified IWG AML response criteria (Appendix F), or death due to any cause, whichever occurs first. Subjects without morphologic relapse, progression, or death due to any cause will be censored at the date of the last response assessment. Duration of response will be assessed using Kaplan-Meier methods. Point estimates and 95% CIs will be provided where appropriate for the median and other quantiles.

Time to response is defined as time from the date of first dose to the date of first occurrence of response, which includes CR, CRi, CRp, PR and MLFS as determined by investigator. Time to response will be summarized using descriptive statistics in subjects with documented CR, CRi, CRp, PR and MLFS as determined by the investigator.

For **HRQoL** data, analyses will address the mean differences by treatment group on the EORTC QLQ-C30 scale and subscale scores and the treatment group differences in the proportion of subjects who achieve minimal clinically important differences. EQ-5D-5L will be scored according to the instrument guidance and analyzed accordingly.

[redacted]

Overall survival and one year survival rates will be analyzed using Kaplan-Meier method, and the treatment comparison will be conducted using log-rank test.

The other secondary endpoints include complete remission rate, best overall objecive response rate, rate of hematologic improvement (HI), the sponsor assessed CR/CRh (based on laboratory dataset) and duration of CR/CRh. These endpoints will be analyzed using the statistical methods mentioned above or other statistical methods as appropriate. As noted, CRh is not available from the investigator assessment. As a result, the analyses on CR/CRh will be based on the sponsor derived assessment.

[redacted]

9.7. Safety Analysis

All safety analyses will be performed on the safety population.

Adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Separate tabulations will be produced for all treatment-emergent AEs (TEAEs), treatment-related AEs (those considered by the investigator as at least possibly drug related), SAEs, discontinuations due to AEs, and AEs with at least a Grade 3 severity. By-subject listings will be provided for deaths, SAEs, DLTs, and AEs leading to discontinuation of treatment.

Clinical laboratory results will be listed and summarized descriptively by dose group, which will also include a display of change from baseline. Laboratory values outside of the normal ranges will be identified. Clinically significant laboratory abnormalities that meet Grade 3 or Grade 4 criteria according to the CTCAE version 4.03 will be listed and summarized. Graphical displays of select laboratory parameters over the course of the study may be provided where useful to assist in the interpretation of results.

Descriptive statistics will be provided for ECG intervals and vital sign measurements presented as both actual values and changes from baseline to the post-baseline visit and to the last visit in the study. Electrocardiograms will also be analyzed for QTc intervals, QTc > 480 and > 500, and increase > 30 and > 60 msec.

Tolerability of the study drug will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by subject and summarized.

Subjects in Phase 1b with the same dose level may be pooled with those in Phase 2 for safety presentation as appropriate.

9.8. Interim Analysis

There is no formal interim analysis based on the pre-specified statistical stopping rule and type 1 error rate adjustment. However, the DMC will review data periodically in order to monitor the drug toxicity and treatment inferiority/superiority.

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 on a regular basis. Reports of aggregate data summaries and individual subject data listings, as appropriate, will be prepared for the DMC members for each scheduled meeting. Operational details for the DMC will be detailed in the DMC charter.

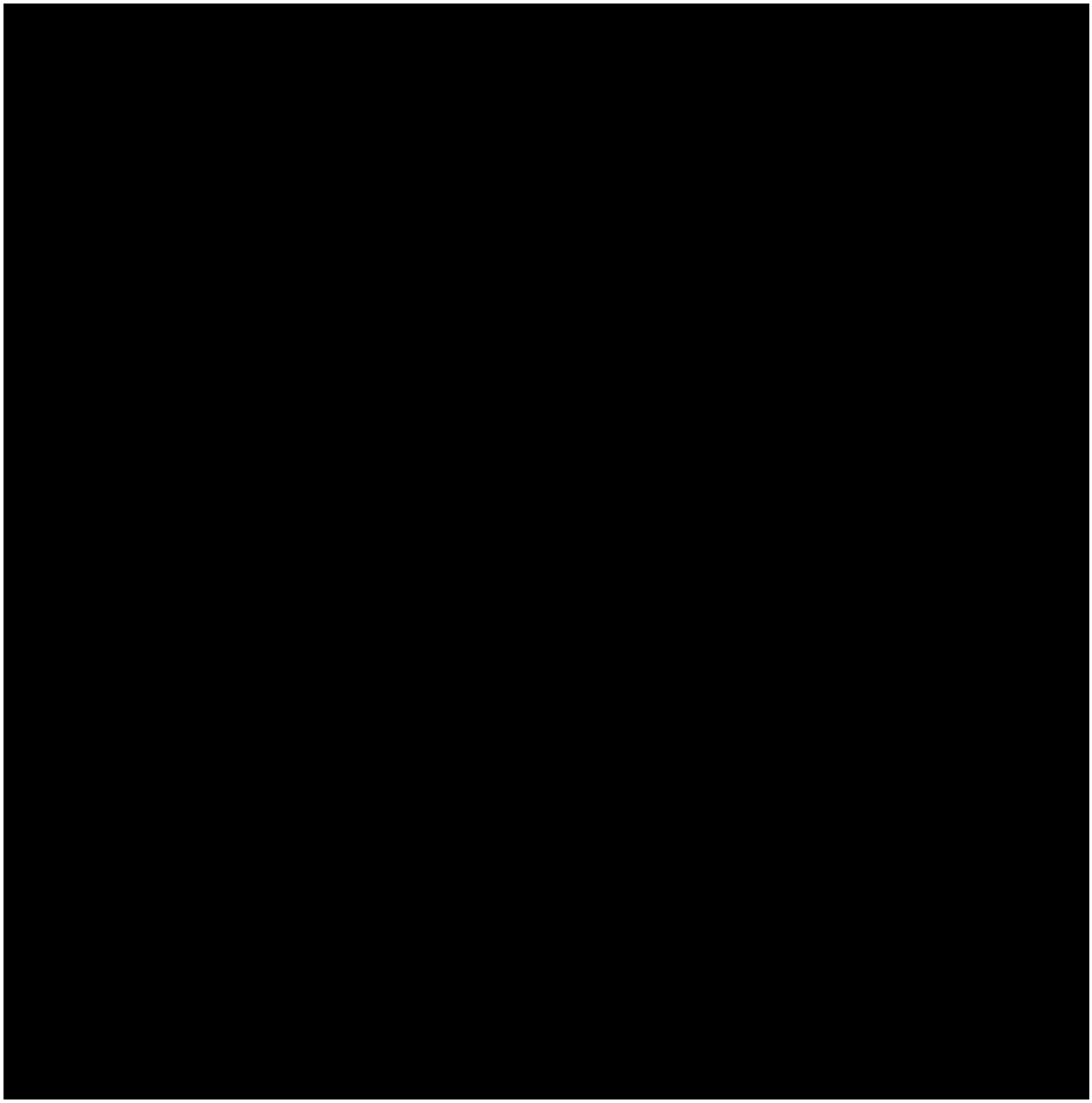
For efficacy data, the DMC will initially review ORR, DOR, EFS and OS after at least 10 subjects have been enrolled in azacitidine mono therapy arm. The DMC will review efficacy data again after each additional 10 subjects per azacitidine mono therapy arm has been enrolled. The

DMC will also review the safety data periodically and make recommendations at the end of each review based on observed safety and treatment inferiority/superiority.

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.



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 CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to any investigational products 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 CRF. (See Section 7.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of any investigational products should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF 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 AG-221, AG-120, or azacitidine overdose. 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 study treatment as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to any of the drugs in study treatment. AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Drug Safety.

All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of study drug. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up or for suspected cases, until SARS-CoV-2 infection is ruled out.

10.2. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events 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 CRF. 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 CRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome for each individual drug in study treatment.

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

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 adverse event 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 adverse event. 'Reasonable possibility' means there

is evidence to suggest a causal relationship between the IP and the adverse event.

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 IP 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 serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. 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 an elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on the investigational product, or within 4 months of the subject's last dose of investigational product, are considered immediately reportable events. All investigational products are to be discontinued immediately. 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 may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.]

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 investigational product 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 investigational product becomes pregnant while the male subject is on study treatment, or within 4 months of the male subject's last study treatment (6 months following the last dose of azacitidine in Canada), the male subject taking study treatment should notify the investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. Where applicable, the study treatment 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 serious criterion requires reporting as an SAE within 24 hours of the investigator's knowledge of the event. 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 are accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study treatment) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of study treatment) or any SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the eCRF, but do not require reporting to Celgene Drug Safety.

The SAE is reported directly to Celgene Drug Safety by facsimile, or other appropriate method using the SAE Report Form or approved equivalent form. 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, results of the autopsy report and/or death certificate are to be reported to Celgene Drug Safety as soon as these become available. Any follow-up data, including responses to safety queries, 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, AG-120, and azacitidine based on their Investigator Brochures.

In the United States, expedited reports sent to the FDA by the sponsor based on the reasonable possibility threshold are known as 'IND safety reports' and will be reported in an expedited manner in accordance with 21 CFR 312.32. For reporting to the FDA, events that are not suspected to be causally related to [AG120, AG-221, azacitidine by the sponsor will not be considered adverse reactions.

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 investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

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 expected adverse events 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:

- 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

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
- Discontinuation of all study drugs
- Death
- Lost to follow-up
- Allogeneic HSCT
- Pregnancy
- Other (to be specified on the eCRF)

The discontinuation of AG-120, AG-221, or azacitidine for subjects treated with the combination is allowed. Subjects may continue treatment with single agent AG-120, AG-221, or azacitidine if in the investigator's assessment the subject continues to show clinical benefit and all protocol-specified criteria for continuing study treatment are met.

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.

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 Follow-up Period of the study (Section 6.3). Every attempt should be made to collect all data during the Follow-up Period unless subjects discontinue from the study.

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

- Screen failure
  - IDH1 / IDH2 mutation negative
  - Other
- Withdrawal (ICF) 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 CRF and in the source documents.

[redacted]

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 informed consent form (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 CRFs 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/EC 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.

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

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

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the 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 adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

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).

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 CRFs or CD-ROM.

14.2. Data Management

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

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 subinvestigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

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

All study documents should be made available if required by relevant health authorities. Investigator 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, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator.

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

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

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, CRFs and applicable supporting records of study subject participation for audits and inspections by IRBs/ECs, regulatory authorities (eg, Food and Drug Administration, European Medicines Agency, 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.

15.3. Investigational Medicinal Product Quality Issues

Issues that call into question IP safety, purity, potency, quality and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to the study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all sponsor supplied IP suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or

distribution). This includes suspected quality issues of components co-packaged with the drug, labelling, and IP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps). When reporting, provide as much product information as possible. Suspected IP quality issues will be investigated and a response will be provided back to the investigational site.

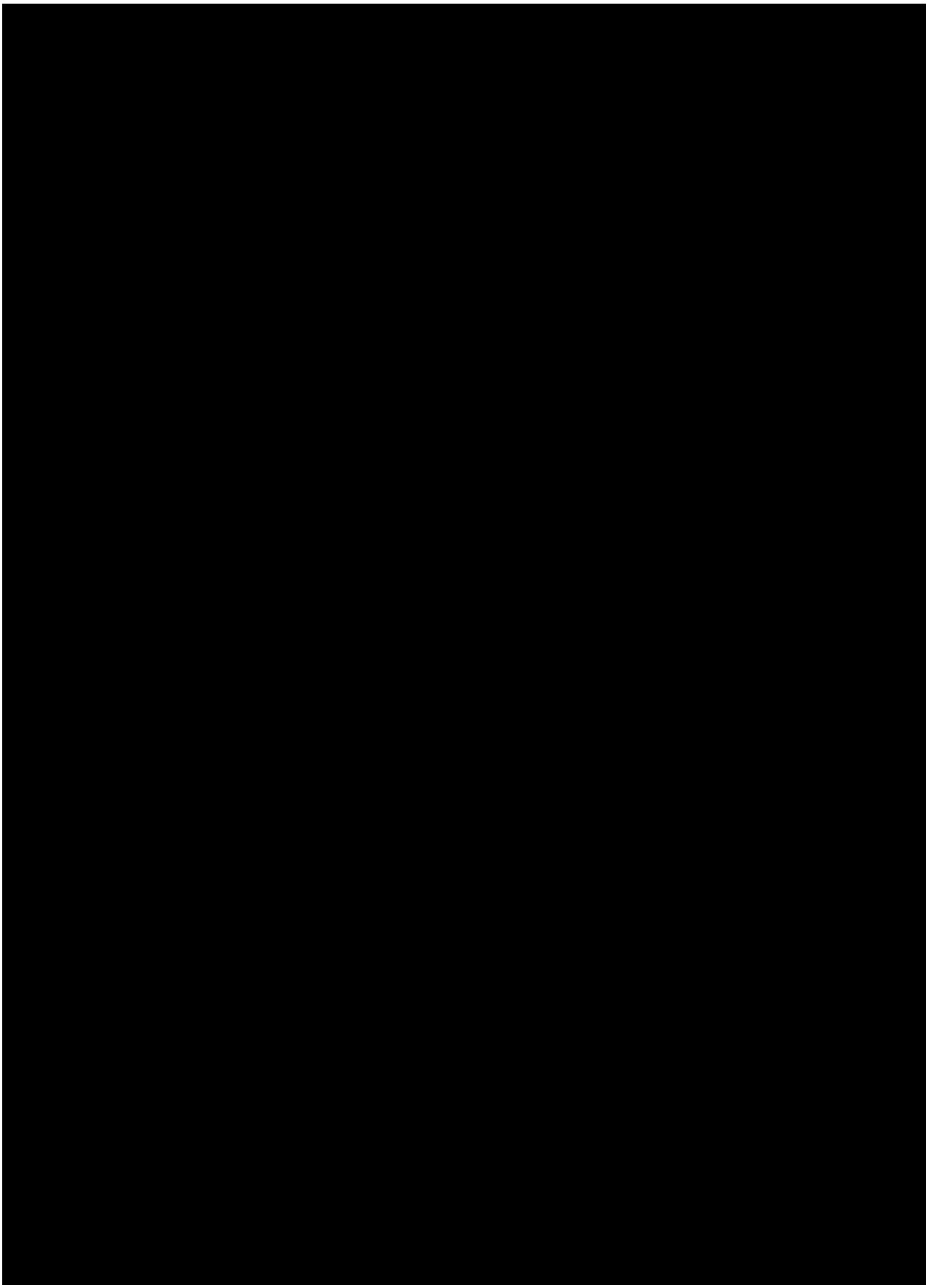
16. PUBLICATIONS

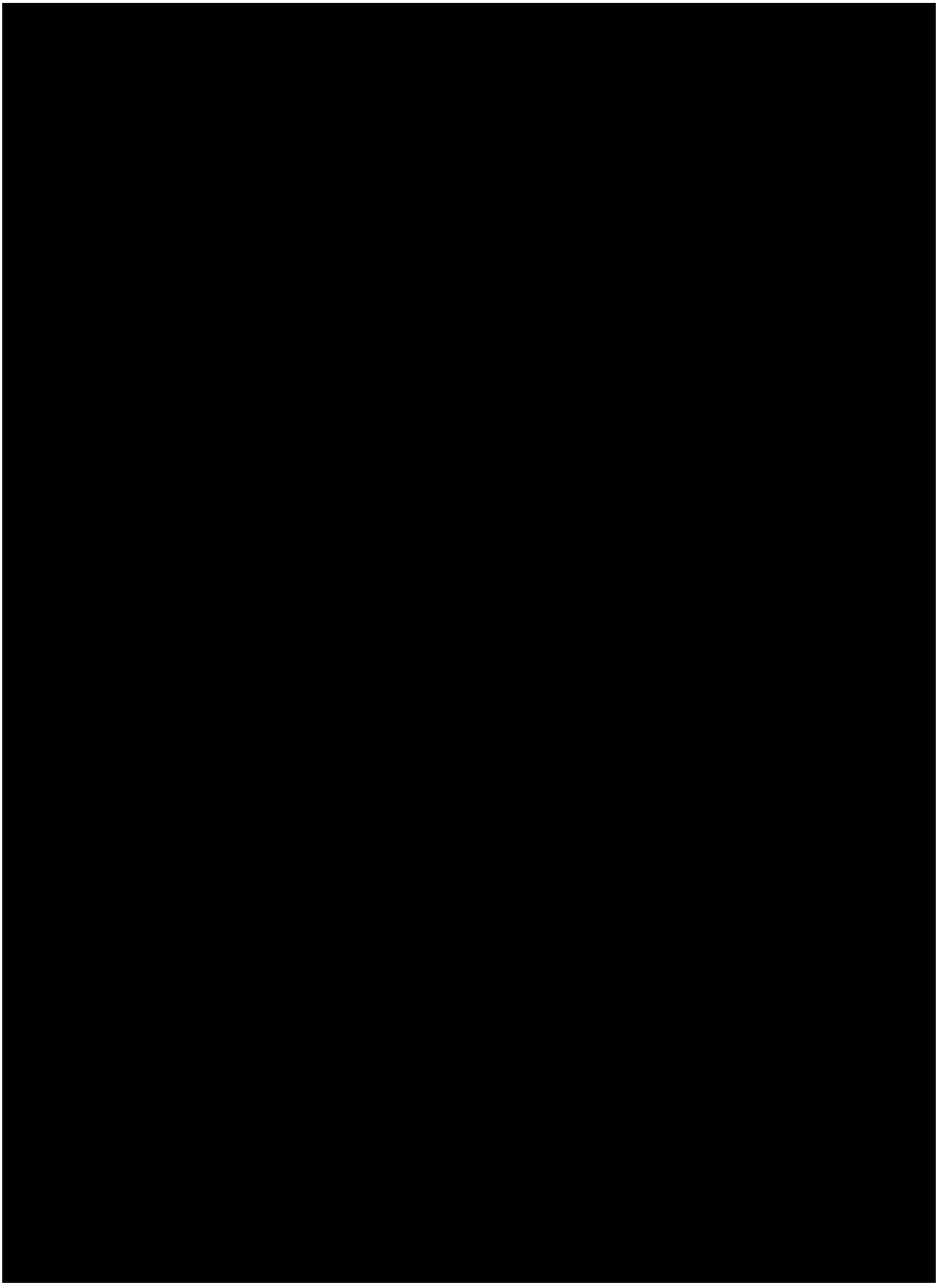
As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed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

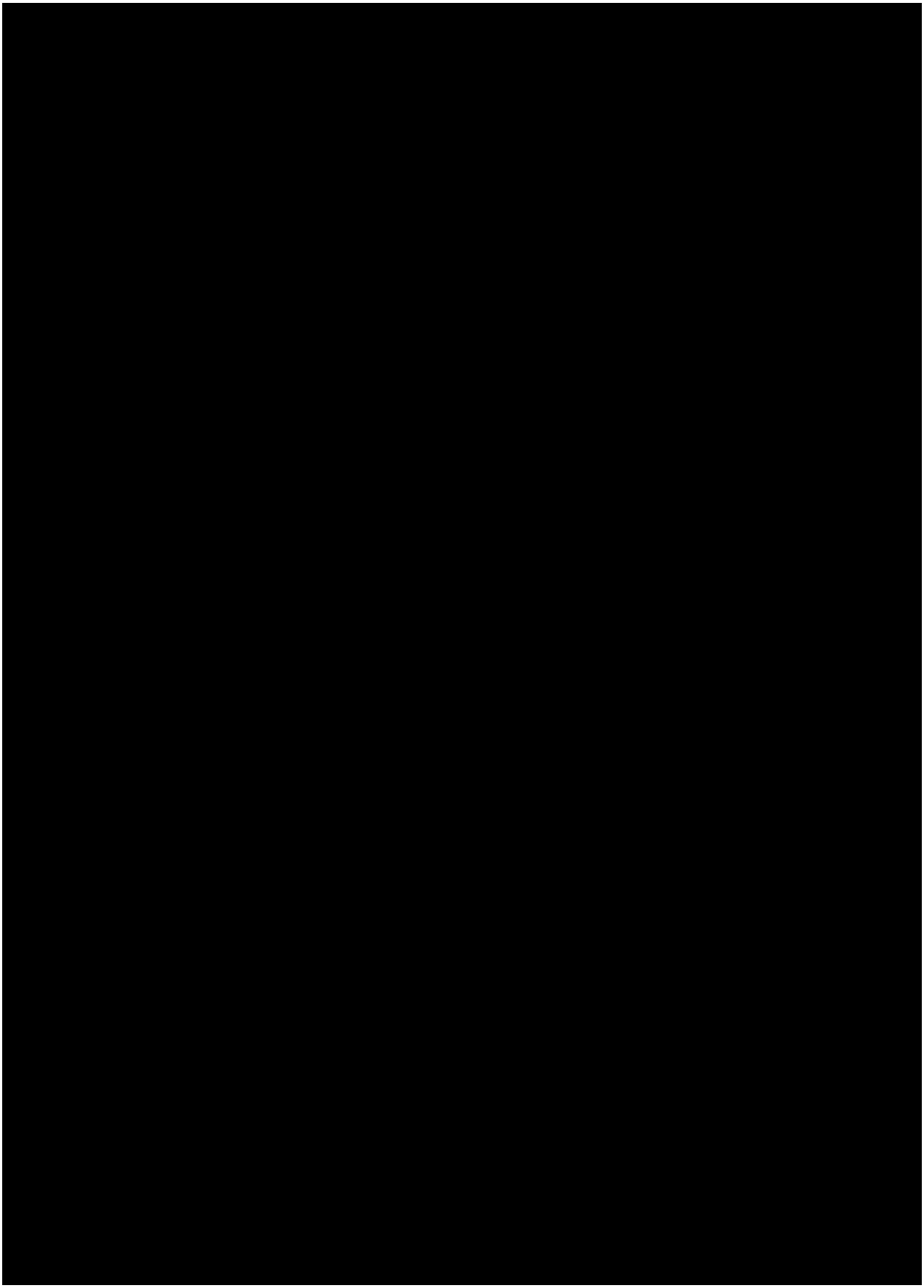
Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This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

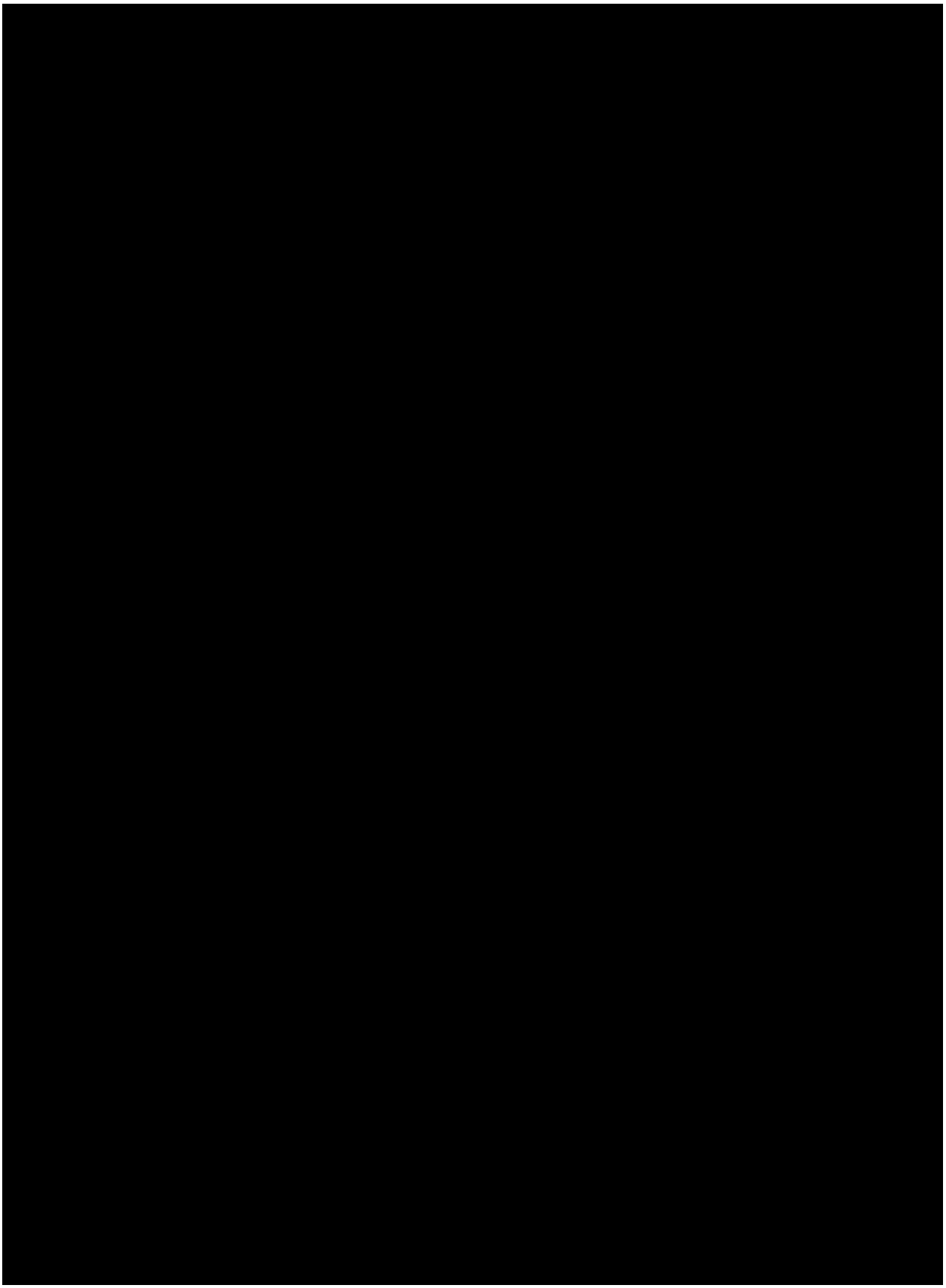
Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority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

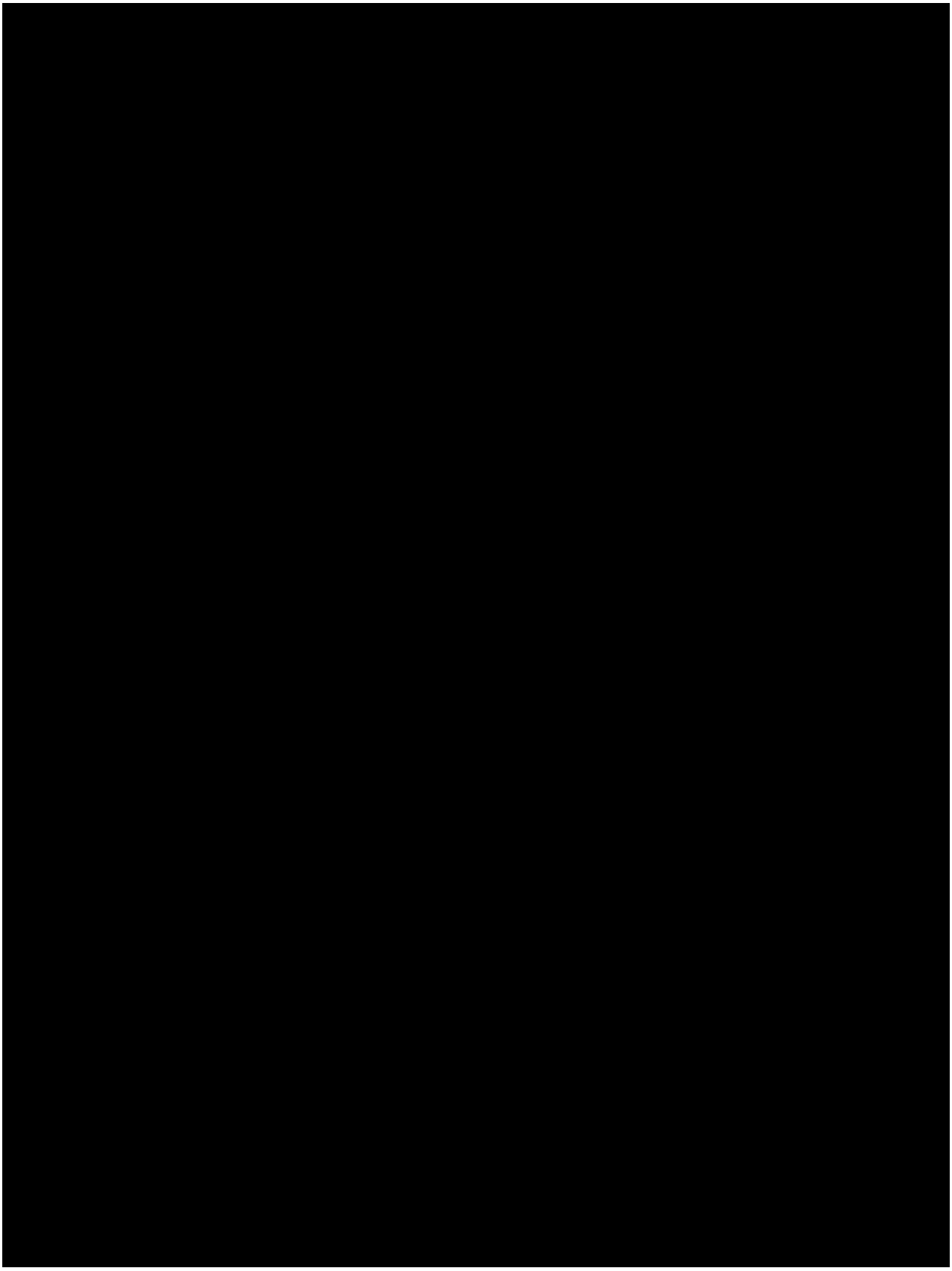
Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when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











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18. APPENDICES

Appendix A: Table of Abbreviations

Abbreviation or Specialist Term	Explanation
AE	Adverse event
[redacted]	
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
BCRP	Breast cancer resistance protein
[redacted]	
BM	Bone marrow
BSA	Body surface area
BSC	Best supportive care
CML	Chronic myelogenous leukemia
CO_2	Carbon dioxide
CR	Morphologic complete remission
CRi	Morphologic complete remission with incomplete neutrophil recovery
CRp	Morphologic complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DDS	Dose Determining Set
[redacted]	
DMC	Data Monitoring Committee
DRT	Dose Review Team
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Appendix A: Table of Abbreviations (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	
EFS	Event-free survival
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
FAP	Full analysis population
FCBP	Female of childbearing potential
GCP	Good Clinical Practice
[redacted]	
HBV	Hepatitis B virus
2-HG	2-hydroxyglutarate
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
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
IC	Inductive chemotherapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IDH1	Isocitrate dehydrogenase 1
IDH2	Isocitrate dehydrogenase 2
IND	Investigational New Drug
IP	Investigational product
IRAC	Independent Response Adjudication Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenously
IWG	International Working Group
IWRS	Interactive web response system

Appendix A: Table of Abbreviations (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	
MDS	Myelodysplastic syndrome
mITT	Modified intent-to-treat
MLFS	Morphologic leukemia-free state
MPN	Myeloproliferative neoplasm
[redacted]	
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
[redacted]	
NIP	Non-investigational product
OAT	Organic anion transporter
[redacted]	
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
[redacted]	
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PO	Orally
PR	Partial remission
QD	Once a day
QTc	Heart rate-corrected QT
[redacted]	
QTcF	QTc with Fridericia's correction
RBC	Red blood cell
RCD	Recommended Combination dose
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous

Appendix A: Table of Abbreviations (Continued)

Abbreviation or Specialist Term	Explanation
SD	Stable disease
SDev	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
[redacted]	
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
[redacted]	
UGT1A1	UDP-glucuronosyltransferase 1 family, polypeptide A1
ULN	Upper limit of normal
[redacted]	
WBC	White blood cell
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 neoplasm

Acute myeloid leukemia, not otherwise categorized

Acute myeloid leukemia with minimal differentiation

Acute myeloid leukemia without maturation

Acute myeloid leukemia with maturation

Acute myelomonocytic leukemia

Acute monoblastic and monocytic leukemia

Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Appendix C: Acute Myeloid Leukemia Risk Status

Risk Status	Cytogenetics	Molecular Abnormalities[a]
Better-risk	inv(16)[b] [redacted] 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.

[redacted]

[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

[redacted]

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

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

[redacted]

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.

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 morphologic 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 morphologic CR except the following: • Platelet count < 100 x 10^9/L (100,000/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 morphologic 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 cells from BM
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 post-treatment 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. CRh = morphologic complete remission with partial hematologic recovery: defined as less than 5% blasts in a BM aspirate sample with marrow spicules plus ANC > 500 x 109/L (1,000/μL) & Platelet count > 50 x 109/L (100,000/μL).

[a] Modification to IWG response criteria.

[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.

[redacted]

Appendix G: 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 [redacted] 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.

[redacted]

Appendix H: 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:

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

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

4. Reconstitute.
5. Place in refrigerator immediately (2°C to 8°C). Product may be held under refrigerated conditions for a maximum of 8 hours.
6. When ready to administer, remove from refrigerator. If elapsed time held in refrigerator is greater than 8 hours, the suspension should be discarded appropriately and a new dose prepared.
7. 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).
8. 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.

Nurse or doctor must administer dose to subject.

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

Preparing the suspension for subcutaneous administration:

9. 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.
10. Document the sequence number of vial(s) on the source document.
11. Wash and dry hands and put on gloves.
12. Remove the syringe from its protective wrapper by peeling back the paper label.
13. 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.
14. 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.
15. Remove the plastic cap from the 18-gauge needle and attach to the syringe. Never touch the needle.
16. Pull the plunger back to the 4 mL mark to draw air into the syringe.
17. Insert the needle through the rubber top of the sterile water vial and push the plunger all the way in.
18. 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.
19. Pull the needle/syringe out of the vial and set the vial down.
20. 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.

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;

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

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).

21. 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.
22. Pull the needle/syringe out of the vial. Properly dispose of the needle according to local pharmacy standard operating procedures and other applicable guidelines.
23. 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**.
24. 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.

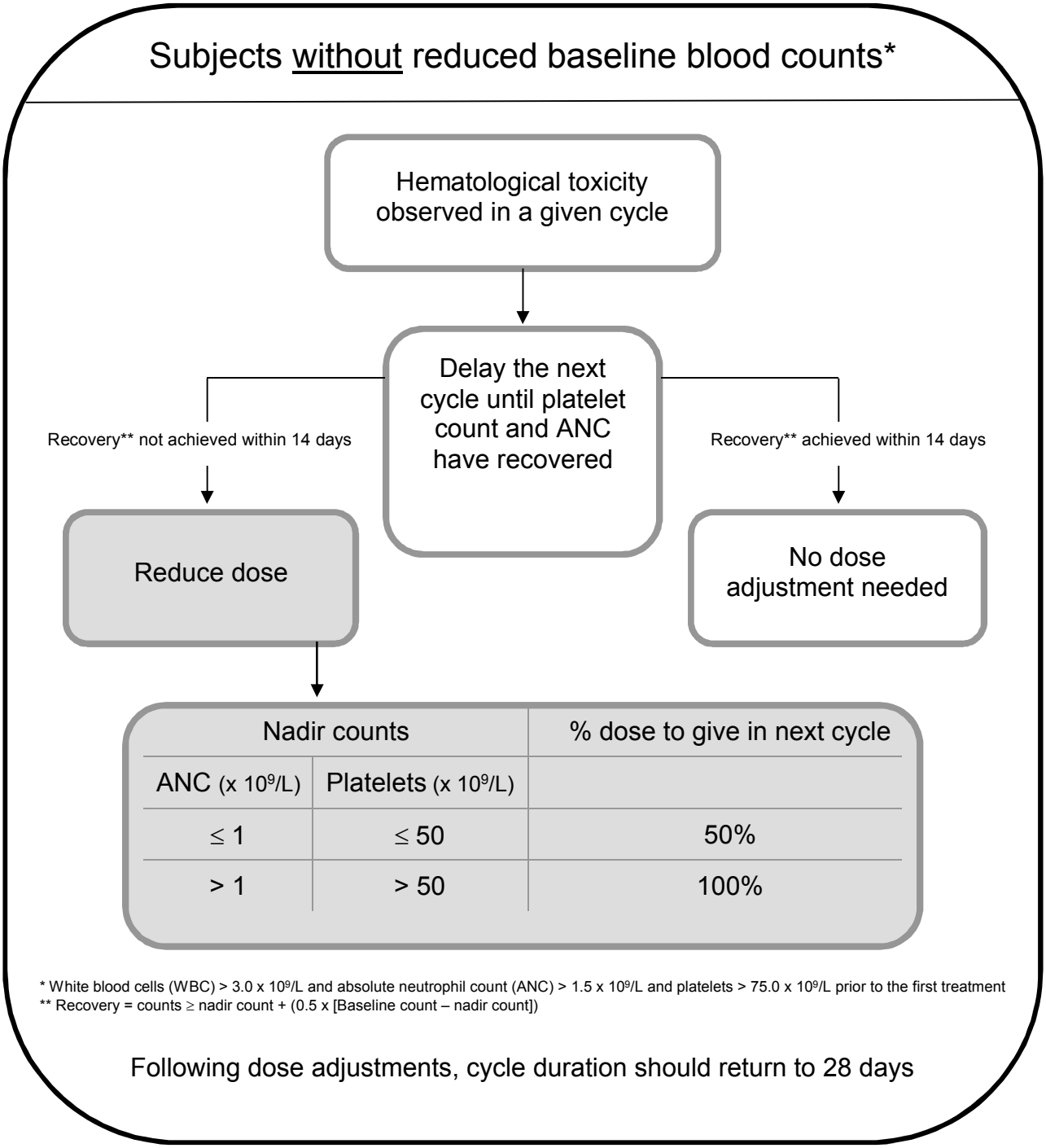
Subcutaneous injection of suspension

25. 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.
26. Rub the area with a fresh alcohol wipe in an outward circular motion.
27. Remove the plastic cap from the subcutaneous needle, being careful to not touch the needle.
28. Pinch a 2-inch fold of skin at the injection site between your thumb and forefinger.
29. Insert the needle at a 90° angle until it is completely inserted.
30. 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.
31. If no blood appears in the syringe, push the plunger forward and inject the drug.

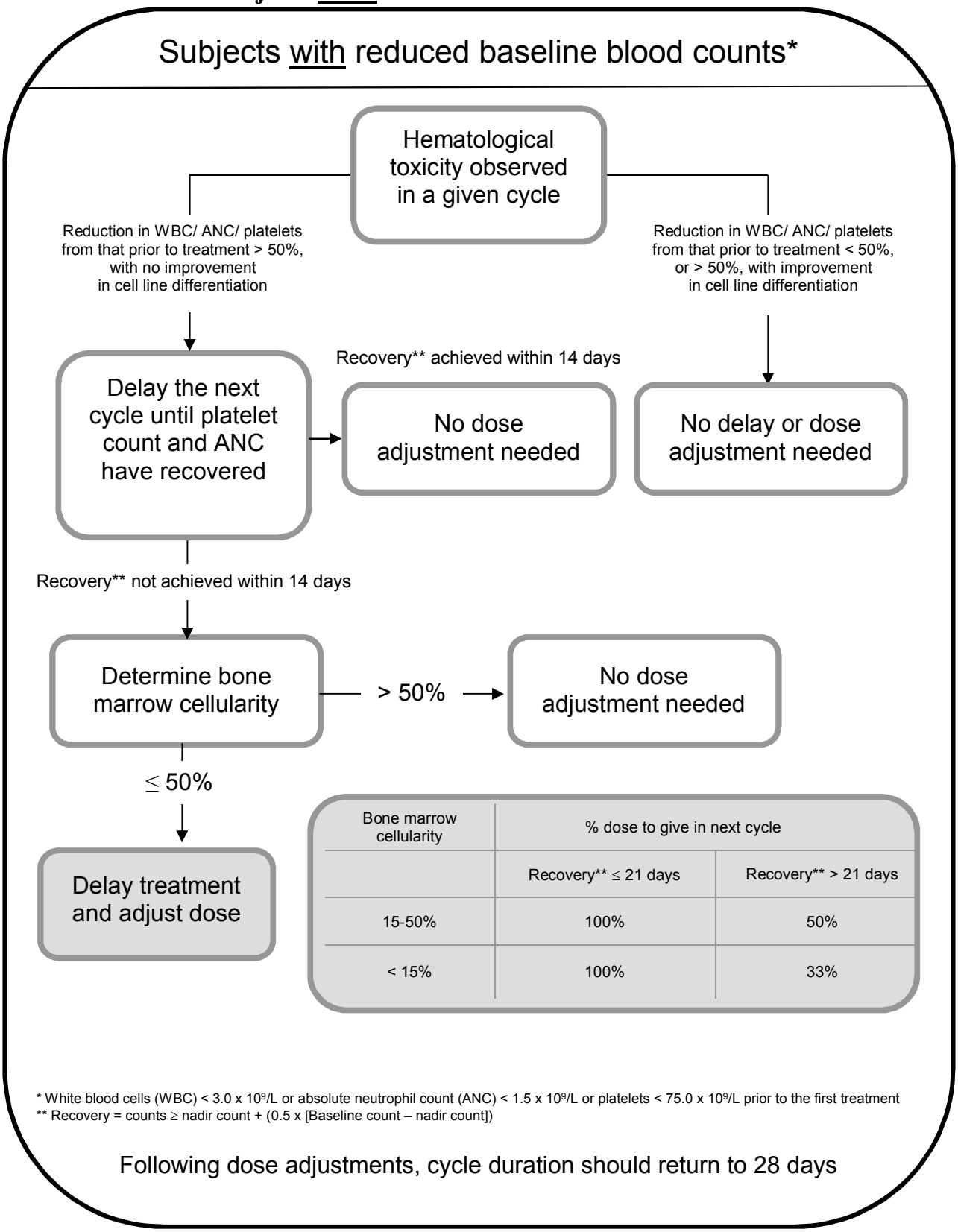
Appendix H: Subcutaneous Preparation and Administration of Azacitidine (Continued)

32. Withdraw the syringe and swab the area with alcohol.
33. 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.
34. 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.
35. Appropriately dispose of all needles and syringes in accordance with local requirements.

Appendix I: Azacitidine Dose Modifications due to Hematologic Toxicity – Subjects Without Reduced Baseline Blood Counts



Appendix J: 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
** Recovery = counts ≥ nadir count + (0.5 x [Baseline count – nadir count])

Appendix K: Cytochrome Sensitive Substrates

From Food and Drug Administration 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, docetaxel
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 Feb 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 (eg, Torsades de Pointes).

[d] The area under concentration (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 Organic anion transporter (OAT)P1B1, 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 (eg, darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-glycoprotein (P-gp).

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

Appendix L: Transporter Sensitive Substrates

From the Food and Drug Administration Drug Development and Drug Interactions Website: Table 13. Examples of In Vivo Substrates for Selected Transporters[a] (7/28/2011)		
Transporter	**Gene**	**Substrate**
P-glycoprotein (P-gp)	ABCB1	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
Breast cancer resistance protein (BCRP)	ABCG2	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

[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

Appendix M: Medications Known to Prolong the QT Interval

amiodarone	citalopram	Escitalopram	methadone	sevoflurane
astemizole	clarithromycin	Flecainide	moxifloxacin	sotalol
azithromycin	disopyramide	Halofantrine	pentamidine	sparfloxacin
bepridil	dofetilide	Haloperidol	pimozide	terfenadine
chloroquine	domperidone	Ibutilide	probucol	thioridazine
chlorpromazine	droperidol	Levomethadyl	procainamide	
cisapride	erythromycin	Mesoridazine	quinidine	

Appendix N: European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (Version 3.0) [redacted]

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: [redacted]
Your birthdate (Day, Month, Year): [redacted]
Today's date (Day, Month, Year): 31 [redacted]

		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 N: European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (Version 3.0) [redacted] (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 O: EQ-5D-5L Health Questionnaire (English Version for the United Kingdom) [redacted]

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 ❑

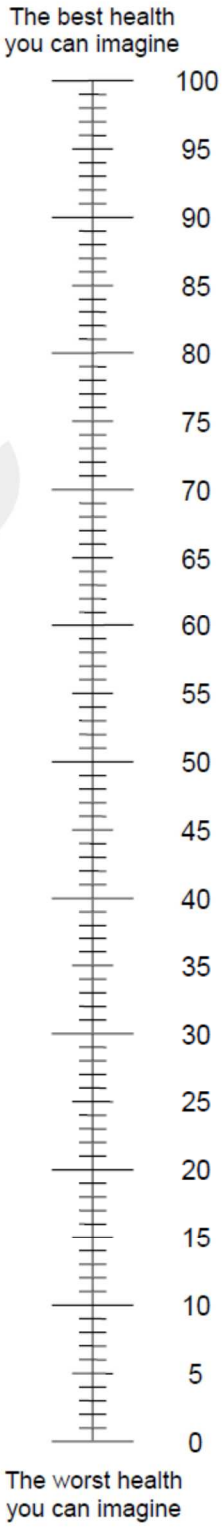
ANXIETY / DEPRESSION

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 O: EQ-5D-5L Health Questionnaire (English Version for the United Kingdom) [redacted] (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 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: Thursday, 13 May 2021, 05:30 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

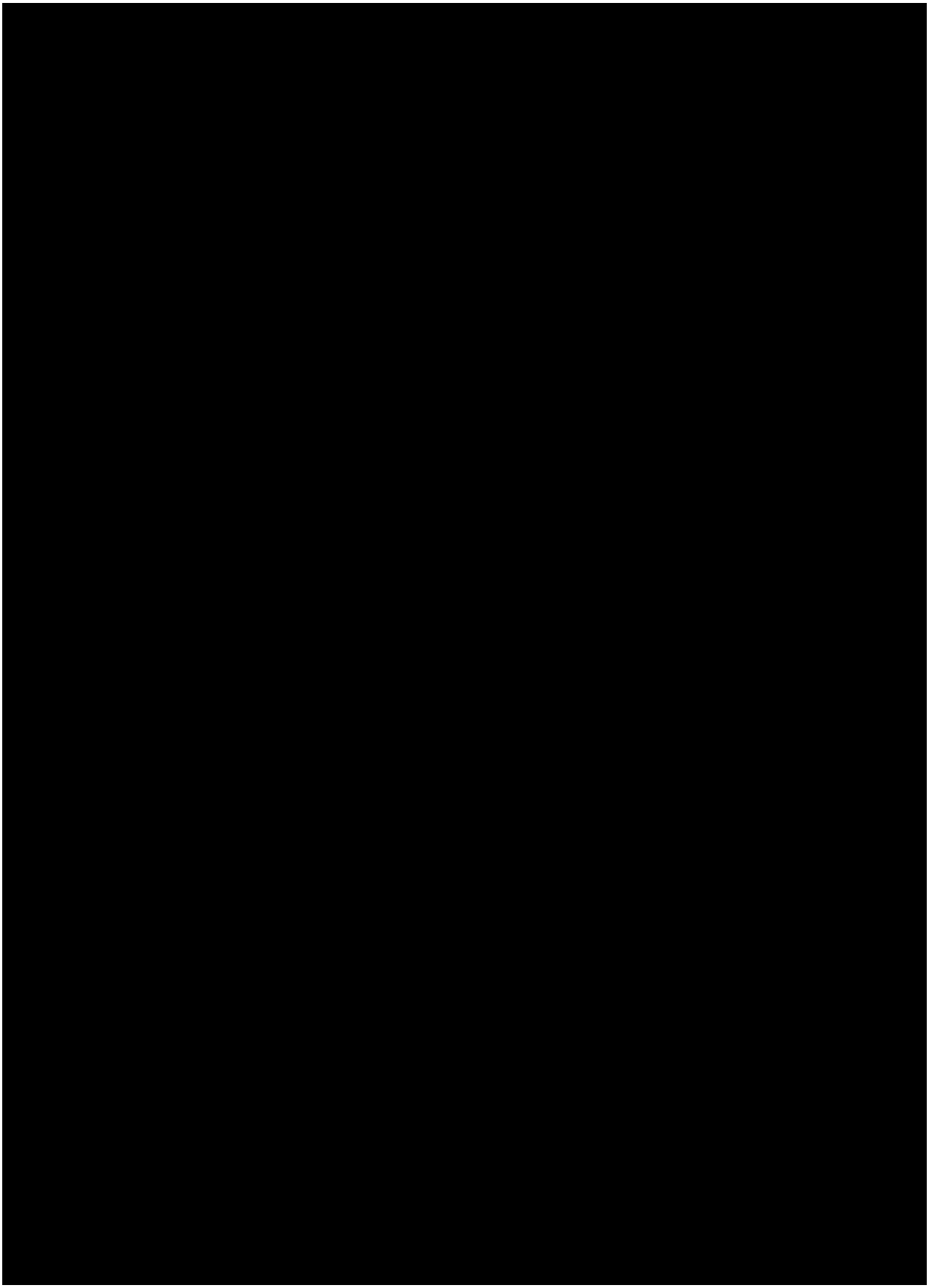
Key changes included in this amendment are summarized below:

- **Protocol modified to allow subjects on treatment to continue as long as they receive clinical benefit and to collect minimal safety, efficacy and survival information.**

  As of 15 Dec 2020, the primary analysis Clinical Study Report (CSR) for this study with 12-month follow-up data (data cutoff of 19 Aug 2019) was finalized and additionally, 24-month follow-up data (data cutoff of 19 Aug 2020) with mature duration of response, median event-free survival (mEFS) and updated overall survival (OS) was made available in use for an interim Data Monitoring Committee (DMC) meeting indicating that no further data is needed to support the endpoints defined in the protocol for the Phase 1b and Phase 2.

  As of 15 Mar 2021, there are only 15 subjects who remain on treatment (4 receving AG-120 plus Azacitidine and 11 receiving AG-221 plus Azacitidine) and 16 in the Follow-up phase under Amendment 02. [redacted]

[redacted]



[redacted]

Section 8.3. Permitted Concomitant Medications and Procedures

– Added guidance for COVID-19 vaccines that can be administered

Section 8.4. Prohibited Concomitant Medications and Procedures

- Added guidance for COVID-19 vaccines that should generally not be administered

[redacted]

Section 10.1 Monitoring, Recording and Reporting of Adverse Events

- Updated this section to align with the current protocol template language.
- Included information regarding collection of SARS-CoV-2 infection AE/SAEs, reporting and monitoring details.

Section 10.5 Reporting of Serious Adverse Events

- Updated the SAE reporting language to align with the current protocol template.

Section 10.6 Expedited Reporting of Adverse Events

- Updated the expedited adverse event reporting language to align with the current protocol template.

[redacted]

Section 15.1 Study Monitoring and Source Data Verification

- Updated the site monitoring language to align with the current protocol template.

Section 15.3 Investigational Medicinal Product Quality Issues

- Added this section as it was missing in the template version that was used to create this protocol amendment.

Minor changes included in this amendment are summarized below:

- Updated contact details for the medical monitor for the AG-221-AML-005 study.
  Revised Sections: Medical Monitor / Emergency Contact Information
- Therapeutic Area Head and the title were updated
  Revised Section: Signature page
- Protocol Summary Overview of Key Efficacy Assessments and Section 6.5.2 Hematologic Improvement:
  - Updated the protocol to reflect that disease response and hematologic improvement will be assessed retrospectively by a blinded Independent Response Adjudication Committee (IRAC) if the study data will be used for regulatory activities while previously the protocol stipulated that this would only be done for hematologic improvement.

[redacted]

- Added new abbreviations “IRAC” and “SoC” to the List of Abbreviations and updated definition for “International Council for Harmonisation (ICH).”
- Minor formatting, editorial changes and corrections were made throughout this document

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. **Modification of the Phase 1b / 2 study design**

   Celgene has transfer of global development rights for AG-120 (IDH1 inhibitor) to Agios in May 2016, the study was redesigned to expand the number of patients analyzed during the Phase 1b stage of the study to determine a safe and effective dose of AG-120 administered with azacitidine for future studies. Consequently, AG-120 administered with azacitidine was removed from the Phase 2 stage of the study.

   The Phase 1b (AG-120 expansion) stage will evaluate the safety, tolerability, and clinical activity of oral AG-120 when administered with Subcutaneous azacitidine.

   The Phase 2 stage of the study will no longer include AG-120 administered with azacitidine (IDH1 subjects) as well as the IDH1 patient included in the azacitidine alone arm.

   Revised Sections: Protocol Summary, [redacted] 3.1, 3.1.1.4, 3.1.2, 3.1.2.2, 3.1.2.5 (Figure 3 and Figure 4), 4.1, 5 (Table 4, 5, 6, 7), 5 (Table 4) footnote ee, 6.2, 6.6, 7.2.1.1, 7.2.2.1, 7.2.2.1.2, 7.2.2.2, 7.3, 9.1, 9.2.1, 9.2.2, 9.3, 9.6, 9.8, 9.9.1, 11.1

2. **Modification of efficacy response endpoints**

   Based on evolving discussions with regulatory agencies, evaluations of response and their interpretation of clinical benefit has evolved as described by the update of overall response and other clinically meaningful endpoints.

   Revised Sections: Protocol Summary, 2 (Table 2), 5 (Table 4) footnote v, 6.2, 9

3. **Statistical assumptions have changed to reflect the addition of the expansion arm in Phase 1b and the deletion of AG-120 in Phase 2**

   The power for the trial has been updated to reflect the changes to the study design.

   Revised Sections: Protocol Summary, 9

Minor changes included in this amendment are summarized below:

- Updated contact details for the medical monitor for the AG-221-AML-005 study.

  Revised Sections: Medical Monitor / Emergency Contact Information

- An administrative change was made where applicable to update “harboring” to “with”.

  Revised Sections: Global change

- An administrative change was made where applicable to update “in combination with” to “administered with” regarding the administration of AG-120 and AG-221 with azacitidine.

  Revised Sections: Global change

- Based on the change in the study design AG-120 administered with azacitidine is no longer part of the phase 2 segment so the term “recommended phase 2 dose” no longer applied and was changed to “recommended combination dose”.

Revised Sections: Global change

- Hematologic improvement is an end point defined for myelodysplastic patients but is also associated with clinical improvement in acute myeloid leukemia, it's use in this disease state has been clarified.

  Revised Sections: Protocol Summary

- An administrative change was made where applicable to update the timeframe for which AG-120 and AG-221 should be taken in relation to the dose taken on the previous day.

  Revised Sections: Protocol Summary

[redacted]

- The Pharmacodynamic [redacted] have been updated to clarify the [redacted] assessment schedule, and procedures to increase compliance and simplify the collection the necessary pharmacodynamic samples [redacted]

  Revised Sections: [redacted] 5 (Table 4, footnote aa, footnote hh), 6.7

- A clarification was added that all trans retinoic acid (ATRA) for suspected APL is not considered prior systemic anticancer therapy.

  Revised Sections: 4.3

- Given the lower incidence of IDH1 mutation in subjects with AML and based on feedback from participating sites, the exclusion of prior use of azacitidine has been modified to allow subjects to use a pre-study dose of one cycle of azacitidine.

  Revised Sections: Protocol Summary, 3.1, 3.1.1.6, 3.1.2.2, 4.1, 4.2, 4.3, 9.1

- Updated AG-120 and AG-221 efficacy and safety data is available based on the current Investigator's Brochure.

[redacted]

Revised Sections: 3.1

- Due to a typographical error the symbol for less than or equal to was added to inclusion criteria number 6.

  Revised Sections: 4.2

  Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR) is felt to be a more appropriate for the evaluation of creatinine clearance. Revised Sections: 4.2

- Pregnancy prevention language has been updated to clarify acceptable forms of birth control as well as parameters for pregnancy testing in males and females. This update is based on Clinical Trial Facilitation Group Recommendations related to contraception and pregnancy testing in clinical trials and was made based on a regulatory request for this study. There were no new nonclinical findings that led to the additional text in inclusion criteria.

  Revised Sections: 4.2

- The use of hydroxyurea will be allowed for all subjects with leukocytosis in order to control peripheral leukemic blasts, and the use of all trans retinoic acid (ATRA) for suspected acute promyelocytic leukemia is clarified as not exclusionary.

  Revised Sections: 4.3

- Hematologic improvement is a secondary endpoint for this trial. Details are provided to assist with the collection of transfusion taking place outside of the investigational site.

  Revised Sections: 5 (Table 4), 6.2, 6.2.3, 6.3

- Administrative change to make footnote p consistent with section 6.3.

  Revised Sections: 5 (Table 4) footnote p

  - A clarification was added to identify what assessments are specific to Cycle 2 Day 1 and Cycle 3 Day 1.

  Revised Sections: 5 (Table 4) footnote w and x

- Three cardiac markers are not required to check cardiac function. Only troponin T will be assessed.

  Revised Sections: 6.2

- Guidelines requiring fasting for AG-120 were included in the protocol in error. An update has been made to clarify that fasting is only required for AG-221.

  Revised Sections: Protocol Summary, 7.2.1.1

- Data indicates that's AG-120, AG-221, azacitidine could take anywhere from 4 to 6 cycles before the first response.

  Revised Sections: 7.2.1.1, 7.2.1.2

- Clarifications were made to allow for continuous AG-221 treatment cycles without delays due to disease-related hematologic toxicities.

  Revised Sections: 7.2.2.2.2

- Global guidelines for the consistent treatment of IDH Differentiation Syndrome and Abnormal Level of Liver Enzymes have been proposed as well as a clarification to define two circumstances for reference hematologic toxicities.

  Revised Sections: 7.2.2.2.2

- No new treatment should be initiated while participating in this trial in order to not confound the efficacy results of the trial.

Revised Sections: 8.4

- The trial will not be run in Japan so the reporting guidelines for Japan were removed.

  Revised Sections: 10.6

[redacted]

- A guideline was added as an example of acute clinical management.

  Revised Sections: 6.4.2, Appendix P

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. **Modification of pharmacokinetics assessments**

   Intensive and sparse pharmacokinetics samples will not be collected for azacitidine. The pharmacokinetic exposure range of azacitidine has been well investigated previously. Due to the large variability seen with azacitidine monotherapy, it would be hard to formulate any conclusions in this study when compared with azacitidine pharmacokinetic data from other studies.

   Intensive pharmacokinetics samples will not be collected for AG-221 and AG-120 on Cycle 1 Day 1. Intensive pharmacokinetics will only be collected at Cycle 2 Day 1 (at steady state). The current intensive and sparse pharmacokinetic plan for AG-221/AG-120 will provide the necessary information for the exposure range of these drugs as well as data to investigate any unexpected safety findings.

   The reduced number of assessments as well as the alignment of these blood draws with scheduled cycle visits in this elderly frail population will help to improve site and subject compliance while still collecting the necessary PK samples for the study.

   Revised Sections: Protocol Summary, 2 (Table 1), 5 (Table 4, footnote ee; Table 5; Table 6), 6.6, 9.9.3.1

2. **Modification of pharmacodynamics [redacted] assessments**

   Modifying of the bone marrow sampling schedule as well as increasing of the peripheral blood sampling reduces the number of bone marrow samples required from the subjects.

   The reduced number of assessments as well as the alignment of these assessments with other efficacy and safety visits in this elderly frail population will help to improve site and subject compliance while still collecting the necessary pharmacodynamic [redacted] sampling.

   Revised Sections: 5 (Table 4, including footnotes), 6.7, 6.8

3. **Change of the stratification factor from cytogenetic risk to primary (ie, de novo) or secondary (progression of MDS or myeloproliferative neoplasms [MPN], or therapy-related) AML**

   Sample processing requirements along with result times of up to 2 weeks at some centers in this newly diagnosed AML population could negatively impact a subject's ability to enter into this study due to the need to initiate treatment prior to receiving cytogenetic results. For this Phase 1b/2 study, stratification will now be de novo versus secondary AML to limit potential bias related to poorer prognosis and treatment resistance in the secondary AML population.

   Revised Sections: Protocol Summary, 3.1.2, 7.2.2.2, 7.3

4. **Local isocitrate dehydrogenase (IDH) mutation testing is acceptable for inclusion in Phase 2**

   Requirements for central IDH testing for inclusion in the trial have changed to a local requirement for inclusion in order to reduce the potential need to perform multiple bone marrow aspirates/biopsies during the screening process.

   Revised Sections: Protocol Summary, 3.1.2.1, 4.1, 4.2, 5 (Table 4, including footnotes), 6.1

Minor changes included in this amendment are summarized below:

- Pharmacodynamics was always an exploratory objective and has been removed as a secondary objective.

  Revised Sections: Protocol Summary, Table 1

- Due to a typographical error Fisher exact test has been changed to Chi square test to be consistent with Section 9, Statistical Considerations.

  Revised Sections: Protocol Summary

- Wording was changed to clarify the allowable dose limiting toxicities per cohort in order for a dose to still be considered a Phase 2 dose.

  Revised Sections: 3.1.1, 3.1.1.1

- As per Celgene standard dashes were added to blank cells in the Table of Events.

  Revised Sections: 5, Table 4: Table of Events

- The results from this Phase 1b/2 trial will be used to help design a Phase 3 trial, local results and investigator response will be used to assess event-free survival and overall response rate.

  Revised Sections: Protocol Summary, 6.1, 6.2, 6.3, 6.5.1, 9.6.2, 9.9.1

- Additional guidance with regards to the use of best supportive care measures based on feedback received by investigators was added.

  Revised Sections: Protocol Summary, 7.2.1.2

- Preparation of azacitidine will not be recorded in the case report form or source records; sites will follow local standards for the preparation of azacitidine.

  Revised Sections: Protocol Summary, Appendix H

- To be consistent throughout the protocol, subcutaneous (SC) was added when describing azacitidine dosing.

  Revised Sections: Global change

[redacted]

- Throughout the protocol the use of "PD" as the abbreviation for pharmacodynamics was omitted to avoid reader confusion with the use of PD as standard medical terminology in describing progressive disease in this indication.

  Revised Sections: Global change

- In defining DLT-evaluable subjects, "or" was corrected to "and" with regards to minimum dosing requirements of the combination therapy.

  Revised Sections: 3.1, 9.2.1

- Wording regarding females of childbearing potential and males was updated to improve compliance based on recommendations from the EU clinical trials facilitation group and to be in line with label information.

  Revised Sections: 4.2, 10.4.1

- "Subject Status" was added to the "IWRS Registration" line of the Table of Events for clarity.

  Revised Sections: 5 (Table 4)

- Treatment and study duration was reconciled with Section 11.1 and 11.2.

  Revised Sections: 7.2.1.1

- Drug toxicity language has been updated to reflect new data from ongoing clinical and non-clinical studies.

  Revised Sections: 7.2.2.2.2, 7.2.2.2.4

- The initiation of a new cycle of azacitidine has been clarified when drug has been delayed or discontinued.

  Revised Sections: 7.2.2.2.4

- The potential drug-drug interactions and concomitant medication recommendations section was updated to reflect new information from ongoing non-clinical study data.

  Revised Sections: 8.2

- The "Prohibited Concomitant Medications and Procedures" section was added to be in line with the protocol template.

  Revised Sections: 8.4

- An update was made under the reasons for discontinuing treatment to confirm that all study drugs must be discontinued for a subject to meet the criteria for treatment discontinuation.

  Revised Sections: 11.1

- Relapse and the start of second line treatment were added as reasons to stop following response in the follow up phase because the start of a new therapy is considered disease progression and relapse is considered an event.

  Revised Sections: 3.1.1.7, 3.1.2.4, 6.3

- The pharmacokinetics population has been updated to clarify its definition.

  Revised Sections: 9.2.2