Clinical Study Protocol AG221-C-001

A Phase 1/2, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-221 in Subjects with Advanced Hematologic Malignancies with an IDH2 Mutation

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This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I understand that all documentation provided to me by Celgene or its designated representative(s) concerning this study that has not been published previously will be kept in strict confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of Celgene or its designated representative(s) and the IRB/IEC, except where necessary to eliminate an immediate hazard to the subject.

I have read, understood, and agree to conduct this study as outlined in the protocol and in accordance with the guidelines and all applicable government regulations.

Investigator Name (printed)	Investigator Signature	Date

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_____

Investigational site or name of institution and location (printed)

2. SYNOPSIS

Name of Sponsor/Company:
Celgene Corporation

Name of Investigational Product:
AG-221

Name of Active Ingredient:
AG-221 mesylate

Title of Study:
A Phase 1/2, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-221 in Subjects with Advanced Hematologic Malignancies with an IDH2 Mutation

Study Center(s):
Up to 25 study centers will participate in this study, including enrollment into expansion arms.

Phase of Development: 1/2

Phase 1 (Dose Escalation and Part 1 Expansion) Objectives:

Primary

- To assess the safety and tolerability of treatment with AG-221 administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle in subjects with advanced hematologic malignancies.
- To determine a maximum tolerated dose (MTD) or a maximum administered dose (MAD) and/or the recommended Phase 2 dose (RP2D) of AG-221 in subjects with advanced hematologic malignancies.

Secondary

- To describe the dose-limiting toxicities (DLTs) of AG-221 in subjects with advanced hematologic malignancies.
- To characterize the pharmacokinetics (PK) of AG-221 and its metabolite in subjects with advanced hematologic malignancies.
- To characterize the PK/pharmacodynamic (PD) relationship of AG-221 and 2-hydroxygluturate (2-HG).
- To characterize the clinical activity associated with AG-221 in subjects with advanced hematologic malignancies.

Exploratory

- [redacted]

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Name of Investigational Product:
AG-221

Name of Active Ingredient:
AG-221 mesylate

[redacted]

Phase 2 (previously Part 2 Expansion) Objectives:

Primary

- To assess the efficacy of AG-221 as treatment for subjects with relapsed or refractory AML with an IDH2 mutation.

Secondary

- To further evaluate the safety profile of AG-221 in subjects with relapsed or refractory AML with an IDH2 mutation.
- To characterize the pharmacokinetics (PK) of AG-221 and its metabolite in subjects with relapsed or refractory AML with an IDH2 mutation.
- To characterize the PK/pharmacodynamic (PD) relationship of AG-221 and 2-hydroxygluturate (2-HG).

Exploratory

- [redacted]

Methodology:

Study AG221-C-001 is a Phase 1/2, multicenter, open-label, 3-part (Phase 1 dose escalation, Phase 1 Part 1 Expansion, and Phase 2), safety, PK/PD, and clinical activity evaluation of orally administered AG-221 in subjects with advanced hematologic malignancies with an IDH2 mutation.

In the Phase 1 portion, the study includes a dose escalation phase to determine MTD/MAD and/or the RP2D and an expansion phase (Part 1 Expansion) to further evaluate the safety, tolerability and clinical activity of AG-221 in select populations. The Phase 2 portion (previously Part 2 Expansion) will further inform on the efficacy, safety, tolerability and clinical activity of AG-221 in subjects with refractory or relapsed AML with an IDH2 mutation.

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[redacted] to be followed until death, withdrawal of consent, or the end of the study as per Section 11.2.

Number of subjects (planned):

Approximately a minimum of 291 subjects in total is planned to be enrolled in the study (i.e., in the dose escalation, Part 1 Expansion, and Phase 2 portion of the trial).

Assuming that identification of the MTD/MAD requires the evaluation of 13 dose levels/schedules of AG-221 with up to 5 subjects per dose level, with the exception that the MTD/MAD requires 6 subjects, then 66 subjects will be enrolled during the dose escalation part of the study. Additional subjects may be needed for cohort expansion during dose escalation, for the replacement of subjects who are not evaluable for PK/PD, safety, or clinical activity, or for evaluation of alternative dosing regimens other than the planned escalation scheme or the MTD/MAD, to optimize the RP2D and regimen(s). As of April 2015, 5 dose levels (ranging from 30 mg to 150 mg) have been evaluated in the BID schedule and 8 dose levels (ranging from 50 mg to 650 mg) have been evaluated in the QD schedule.

Four cohorts of a minimum of 25 additional subjects in specific hematologic malignancy subsets (total a minimum of 100 subjects) will be enrolled in Part 1 Expansion of the study.

The Phase 2 portion of the trial will enroll approximately 125 subjects with relapsed or refractory AML with an IDH2 mutation. Additional subjects may be needed for the replacement of subjects who are not evaluable for PK/PD, safety, and/or clinical activity, or for evaluation of alternative dosing regimens. The final total sample size may be adjusted according to the observed toxicity rate, and number of subjects enrolled for expanded evaluation.

Diagnosis and main criteria for inclusion:

Inclusion criteria

Subjects must meet all of the following criteria to be enrolled in the study:

1. Subject must be ≥18 years of age.
2. Subjects must have advanced hematologic malignancy including:

   Phase 1/ Dose escalation:

   - Diagnosis of AML according to World Health Organization (WHO) criteria (Appendix 15.1);
     - Disease refractory or relapsed (defined as the reappearance of > 5% blasts in the bone marrow, see Table 7 and Table 8).

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Name of Investigational Product: AG-221
Name of Active Ingredient: AG-221 mesylate

- Untreated AML, ≥60 years of age and are not candidates for standard therapy due to age, performance status, and/or adverse risk factors, according to the treating physician and with approval of the Medical Monitor;

- Diagnosis of MDS according to WHO classification (Appendix 15.2) with refractory anemia with excess blasts (subtype RAEB-1 or RAEB-2), or considered high-risk by the

  Revised International Prognostic Scoring System (IPSS-R) (Appendix 15.3) (Greenberg, et al. 2012) that is recurrent or refractory, or the subject is intolerant to established therapy known to provide clinical benefit for their condition (i.e., subjects must not be candidates for regimens known to provide clinical benefit), according to the treating physician and with approval of the Medical Monitor. (Subjects with other relapsed and/or primary refractory hematologic cancers, for example CMML, who fulfill the inclusion/excluding criteria may be considered on a case-by case basis, with approval of the Medical Monitor.)

Phase 1/ Part 1 Expansion:

- Arm 1: Relapsed or refractory AML (Table 7 and Table 8) and age ≥60 years, or any subject with AML regardless of age who has relapsed following a BMT.
- Arm 2: Relapsed or refractory AML (Table 7 and Table 8) and age <60 years, excluding subjects with AML who have relapsed following a BMT.
- Arm 3: Untreated AML and age ≥60 years that decline standard of care chemotherapy.
- Arm 4: IDH2-mutated advanced hematologic malignancies not eligible for Arms 1 to 3.

Phase 2:

- Diagnosis of AML according to World Health Organization (WHO) criteria (Appendix 15.1) and disease relapsed or refractory as defined by (Table 7 and Table 8):
  - Subjects who relapse after allogeneic transplantation;
  - Subjects in second or later relapse;
  - Subjects who are refractory to initial induction or re-induction treatment;
  - Subjects who relapse within 1 year of initial treatment, excluding patients with favorable-risk status according to NCCN Guidelines (NCCN 2015). Favorable-risk cytogenetics: inv(16), t(16;16), t(8;21), t(15;17).

3. Subjects must have documented IDH2 gene-mutated disease:

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Name of Investigational Product: AG-221
Name of Active Ingredient: AG-221 mesylate

- For subjects in the dose escalation phase and Part 1 Expansion, IDH2 mutation may be based on local evaluation. (Centralized testing will be performed retrospectively).

4. For subjects in the Phase 2 portion of the trial, central testing of IDH2 mutation in samples of bone marrow aspirate **and/or** peripheral blood, is required during screening to confirm eligibility. Subjects must be amenable to serial bone marrow sampling, peripheral blood sampling, and urine sampling during the study.
   - The diagnosis and evaluation of AML or MDS will be made by bone marrow aspiration and biopsy. If an aspirate is unobtainable (i.e., a "dry tap"), the diagnosis may be made from the core biopsy.
   - Screening bone marrow aspirate **and** peripheral blood samples are required for all subjects. A bone marrow biopsy must be collected if adequate aspirate is not attainable unless:
     - A bone marrow aspirate and biopsy was performed as part of the standard of care within 28 days prior to the start of the study treatment; and
     - Slides of bone marrow aspirate, biopsy and stained peripheral blood smear are available for both local and central pathology reviewers;
5. Subjects must be able to understand and willing to sign an informed consent. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent, if acceptable to, and approved by, the site and/or site's Institutional Review Board (IRB)/Independent Ethic Committee (IEC).
6. Subjects must have ECOG PS of 0 to 2 (Appendix 15.5).
7. Platelet count ≥20,000/μL (Transfusions to achieve this level are allowed.) Subjects with a baseline platelet count of <20,000/μL due to underlying malignancy are eligible with Medical Monitor approval.
8. Subjects must have adequate hepatic function as evidenced by:
   - Serum total bilirubin ≤1.5 × upper limit of normal (ULN), unless considered due to Gilbert's disease, a gene mutation in UGT1A1, or leukemic organ involvement, following approval by the Medical Monitor;
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤3.0 × ULN, unless considered due to leukemic organ involvement.
9. Subjects must have adequate renal function as evidenced by:
   - Serum creatinine ≤2.0 × ULN

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Name of Investigational Product: AG-221
Name of Active Ingredient: AG-221 mesylate

OR

- Creatinine clearance >40 mL/min based on the Cockroft-Gault glomerular filtration rate (GFR) estimation:

$$(140 - \text{Age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})/72 \times \text{serum creatinine}$$

10. Subjects must be recovered from any clinically relevant toxic effects of any prior surgery, radiotherapy, or other therapy intended for the treatment of cancer. (Subjects with residual Grade 1 toxicity, for example Grade 1 peripheral neuropathy or residual alopecia, are allowed with approval of the Medical Monitor.)
11. Female subjects with reproductive potential must agree to undergo medically supervised pregnancy test prior to starting study drug. The first pregnancy test will be performed at screening (within 7 days prior to first study drug administration), and on the day of the first study drug administration and confirmed negative prior to dosing and Day 1 before dosing all subsequent cycles.
12. Female subjects with reproductive potential must have a negative serum pregnancy test within 7 days prior to the start of therapy. Subjects with reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy or tubal occlusion or who have not been naturally postmenopausal (i.e., who have not menstruated at all) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Females of reproductive potential as well as fertile men and their partners who are female of reproductive potential must agree to abstain from sexual intercourse or to use two highly effective forms of contraception from the time of giving informed consent, during the study and for 120 days (females and males) following the last dose of AG-221. A highly effective form of contraception is defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization.
13. Able to adhere to the study visit schedule (ie, clinic visits at the study sites are mandatory, unless noted otherwise for particular study visits) and other protocol requirements

Exclusion criteria

Subjects who meet any of the following criteria will not be enrolled in the study:

1. Subjects who have undergone hematopoietic stem cell transplant (HSCT) within 60 days of the first dose of AG-221, or subjects on immunosuppressive therapy post HSCT at the time of screening, or with clinically significant graft-versus-host disease (GVHD). (The use of a stable dose of oral steroids post HSCT and/or topical steroids for ongoing skin GVHD is permitted with Medical Monitor approval.)

Name of Sponsor/Company: Celgene Corporation
Name of Investigational Product: AG-221
Name of Active Ingredient: AG-221 mesylate

2. Subjects who received systemic anticancer therapy or radiotherapy <14 days prior to their first day of study drug administration. (Hydroxyurea is allowed prior to enrollment and after the start of AG-221 for the control of peripheral leukemic blasts in subjects with leukocytosis (white blood cell [WBC] counts >30,000/μL).
3. Subjects who received a small molecule investigational agent <14 days prior to their first day of study drug administration. In addition, the first dose of AG-221 should not occur before a period ≥5 half-lives of the investigational agent has elapsed.
4. Subjects taking the following sensitive cytochrome P450 (CYP) substrate medications that have a narrow therapeutic range are excluded from the study unless they can be transferred to other medications within ≥5 half-lives prior to dosing: paclitaxel (CYP2C8) warfarin, phenytoin (CYP2C9), S-mephenytoin (CYP2C19), thioridazine (CYP2D6), theophylline and tizanidine (CYP1A2).
5. Subjects taking the P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) transporter-sensitive substrates digoxin and rosuvastatin should be excluded from the study unless they can be transferred to other medications within ≥5 half-lives prior to dosing.
6. Subjects for whom potentially curative anticancer therapy is available.
7. Subjects who are pregnant or lactating.
8. Subjects with an active severe infection that required anti-infective therapy or with an unexplained fever >38.5°C during screening visits or on their first day of study drug administration (at the discretion of the Investigator, subjects with tumor fever may be enrolled).
9. Subjects with known hypersensitivity to any of the components of AG-221.
10. Subjects with New York Heart Association (NYHA) Class III or IV congestive heart failure or LVEF <40% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan obtained within approximately 28 days of C1D1.
11. Subjects with a history of myocardial infarction within the last 6 months of screening.
12. Subjects with uncontrolled hypertension (systolic blood pressure [BP] >180 mmHg or diastolic BP >100 mmHg) at screening are excluded. Subjects requiring 2 or more medications to control hypertension are eligible with Medical Monitor approval.
13. Subjects with known unstable or uncontrolled angina pectoris.
14. Subjects with a known history of severe and/or uncontrolled ventricular arrhythmias.

Name of Sponsor/Company:
Celgene Corporation

Name of Investigational Product:
AG-221

Name of Active Ingredient:
AG-221 mesylate

15. Subjects with QTcF (QT corrected based on Fridericia's equation) interval ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome) at screening. Subjects with bundle branch block and a prolonged QTc interval should be reviewed by the Medical Monitor for potential inclusion.
16. Subjects taking medications that are known to prolong the QT interval (see Section 9.12.3) unless they can be transferred to other medications within ≥5 half-lives prior to dosing.
17. Subjects with known infection with human immunodeficiency virus (HIV) or active hepatitis B or C.
18. Subjects with any other medical or psychological condition, deemed by the Investigator to be likely to interfere with a subject's ability to sign informed consent, cooperate, or participate in the study.
19. Subjects with known dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally.
20. Subjects with clinical symptoms suggesting active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid is only required if there is a clinical suspicion of CNS involvement by leukemia during screening.
21. Subjects with immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation.
22. In Phase 2 portion of the trial only, subjects who have previously received treatment with an inhibitor of IDH2.

Investigational product, dosage and mode of administration:

AG-221 (AG-221 mesylate) will be provided as 5, 10, 25, 50, 100, 150 and 200 mg free-base equivalent strength tablets to be administered orally.

Phase 1/Dose Escalation

The first 3 subjects in each cohort in the dose escalation portion of the study and the first 15 subjects in each arm of Part 1 Expansion will receive a single dose of study drug on Day -3; their next dose of study drug will be administered on C1D1 at which time subjects will start daily dosing on Days 1 to 28 in 28-day cycles. Starting with C1D1, dosing is continuous; there are no inter-cycle rest periods. Subjects who are not required to undergo the Day -3 PK/PD assessments will initiate daily dosing with AG-221 on C1D1.

The dose of AG-221 administered to a subject will be dependent upon which dose cohort is open for enrollment when the subject qualifies for the study. The starting dose of AG-221 to be administered

Name of Sponsor/Company:
Celgene Corporation

Name of Investigational Product:
AG-221

Name of Active Ingredient:
AG-221 mesylate

to the first cohort of subjects is 30 mg administered orally twice a day, and the maximum administered dose of AG-221 to be administered is 650 mg administered orally once a day.

Phase 1/Part 1 Expansion and Phase 2

The starting dose of AG-221 recommended for evaluation is 100 mg QD. This is based on the safety, PK, pharmacodynamics and clinical activity of AG-221 observed to date in AG221-C-001. Evaluation of pharmacodynamic response demonstrated sustained reduction in 2-HG plasma levels by Day 1 of Cycle 2 and up to 98% inhibition in most subjects with R140Q mutation at all doses. Increasing dose is associated with higher exposure and inhibition of 2-HG in subjects with R172K mutation. Importantly, preliminary efficacy data of the 44 subjects treated at 100 mg QD has shown an overall response rate of 36.4%. Thus a dose of 100 mg should adequately achieve inhibition of 2-HG in subjects with either R140Q or R172K mutation. Moreover, the safety profile at 100 mg, including ≥ Grade 3, is consistent with that of lower doses.

Intra-subject dose escalation is possible as per criteria in Section 9.7.2.1.

Duration of treatment:

Subjects may continue treatment with AG-221 until disease progression or development of unacceptable toxicity. Subjects who experience disease progression per the applicable response criteria who are, in the opinion of the Investigator, benefiting from treatment may be allowed to continue on study drug with approval of the Medical Monitor.

End of Study:
The End of Study is defined as either the date of the last visit of the last subject to complete the study, 3 years after the first dose of the last subject enrolled into Phase 2, or the date of receipt of the last data point from the last subject that is required for primary and secondary analysis, as pre-specified in the protocol, whichever is the later date.

Reference therapy, dosage and mode of administration:

Not applicable

Criteria for evaluation:

[redacted]

Clinical Activity:

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Name of Investigational Product: AG-221
Name of Active Ingredient: AG-221 mesylate
Serial blood and bone marrow sampling to determine response to treatment based on modified IWG response criteria (Table 7 through Table 10) or other appropriate response criteria based on the malignancy under study.
Statistical methods: Overall response rate (ORR), the primary efficacy endpoint, is defined as the rate of responders including complete remission (CR), CR with incomplete platelet recovery (CRp), marrow CR (mCR) (morphologic leukemia-free state [MLFS] for subjects with AML), CR with incomplete hematologic recovery (CRi), and partial remission (PR). Other measures of clinical activity including complete remission rate (CRR), duration of remission/response, event-free survival, overall survival, and time to remission/response will be summarized. For Phase 1 Dose Escalation/Part 1 Expansion, the efficacy analysis of response rates as assessed by the site Investigators using modified International Working Group (IWG) response criteria (Table 7 through Table 10) will be conducted in Full Analysis Set for each dose level, expansion arm, and overall if appropriate. The analysis of Part 1 expansion arms may also include subjects from the dose-escalation phase who received the same dose/regimen as subjects in the expansion arms and who meet the eligibility criteria of individual arms. For Phase 2 portion of the trial, the primary efficacy analysis of AG-221 will be determined by the Investigators based on modified International Working Group (IWG) response criteria (Table 7 and Table 8). Response will also be assessed retrospectively by an Independent Response Adjudication Committee (IRAC) using the Full Analysis Set (FAS). Key supportive analyses will be based on independent central review of response in FAS. An observed ORR of at least 33.6% in Phase 2 portion of the trial (at least 42 responses in 125 subjects) will result in an exact binomial 95% CI with a lower bound greater than 25%, which is clinically meaningful in this setting and exceeds the ORR expected with available therapies (Roboz, et al. 2014). This will be considered as evidence of clinically significant activity of AG-221. Tabulations will be produced for disposition, demographic and baseline disease characteristics, safety, PK, PD, and clinical activity parameters and will be presented by study phase, dose level, disease, and overall if appropriate. Categorical variables will be summarized by frequency distributions (number and percentages of subjects) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). [redacted] Descriptive statistics will be provided for clinical laboratory, ECG interval, LVEF, and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Shift analyses will be conducted for laboratory parameters and ECOG PS.

Name of Sponsor/Company: Celgene Corporation
Name of Investigational Product: AG-221
Name of Active Ingredient: AG-221 mesylate
Descriptive statistics will be used to summarize PK parameters for each dose group and, where appropriate, for the entire population. The potential relationship between plasma levels of AG-221 and plasma, urine, and bone marrow 2-HG (and/or α-KG) levels will be explored with descriptive and graphical methods. All time to event endpoints will be estimated using Kaplan-Meier methods. Point estimates and 95% CIs will be provided where appropriate. Estimates of the median and other quantiles, as well as individual time points (e.g. 3-month, 6-month, and 12-month rates) will be produced. Other measures of clinical activity will be evaluated for subjects in Phase 2 portion of the trial, including summaries of transfusion requirements and infection rates. The study data will be analyzed and reported based on all subjects' data from the dose escalation and expansion phases up to the time when all subjects have completed at least 6 cycles of treatment regardless of dose interruption or discontinued study drug earlier, or when the follow up is deemed adequate for the assessment of duration of response, whichever is the later date. Any additional data for subjects continuing to receive study treatment or in follow up for HSCT or survival past the data cutoff date for the clinical study report (CSR) will be reported in a final descriptive update at the end of study.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
2-HG	2-hydroxyglutarate
α-KG	Alpha-ketoglutarate
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
aPPT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0\text{-}12hr}$	Area under the concentration-time curve from 0 to 12 hours
BCRP	Breast cancer resistance protein
BMT	Bone marrow transplant
BP	Blood pressure
BUN	Blood urea nitrogen
C1D1	Cycle 1, Day 1
CEAS	Central efficacy analysis set
CI	Confidence interval
CIMP	Cytosine-guanine dinucleotide island methylator phenotype
CLp	Total body clearance
C_{max}	Maximum concentration
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
CpG	Cytosine-phosphodiesterase-guanine
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CRp	Complete remission with incomplete platelet recovery
CRR	Complete remission rate
CV	Cardiovascular
CYP	Cytochrome
DLT	Dose limiting toxicity
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid

Abbreviation or Specialist Term	Explanation
DOCR	Duration of complete remission
DOR	Duration of response
EAS	Efficacy analysis set
$EAUC_{90(0\text{-}12hr)}$	Estimated area under the AG-221 concentration × time curve from 0 to 12 hours that results in sustained 90% tumor inhibition
$EAUC_{97(0\text{-}12hr)}$	Estimated area under the AG-221 concentration × time curve from 0 to 12 hours that results in sustained 97% tumor inhibition
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
EFS	Event-free survival
EOT	End of Treatment
F	Projected human oral bioavailability
FAS	Full analysis set
FLT3/ITD	FMS-like tyrosine kinase 3/internal tandem duplication
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVHD	Graft versus Host Disease
hCG	Human chorionic gonadotropin
hERG	Human ether à-go-go
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HSCT	Hematopoietic stem cell transplant
IC_{50}	Inhibitory concentration, 50%
IC_{90}	Inhibitory concentration, 90%
ICH	International Conference on Harmonization
ICSH	International Council for Standardization in Hematology
IDH, IDH1, IDH2	Isocitrate dehydrogenase protein, 1, 2
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
IND	Investigational New Drug
INR	International normalized ratio
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
IRAC	Independent Response Adjudication Committee
IWG	International Working Group
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MAD	Maximum Administered Dose
mCR	Marrow complete remission
MDS	Myelodysplastic syndrome
MPN	Myeloproliferative neoplasms
MPD	Myeloproliferative disorders
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPM1	Nucleophosmin 1
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PAS	Pharmacokinetic analysis set
PD	Pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Partial remission
PS	Performance status
PT	Prothrombin time
RAEB, RAEB-1, RAEB-2	Refractory anemia with excess blasts, 1, 2
RBC	Red blood cell (count)
RP2D	Recommended Phase 2 dose
QTc	Heart-rate corrected QT interval

Abbreviation or Specialist Term	Explanation
QTcF	Heart-rate corrected QT interval, Fridericia's correction
SAE	Serious adverse event
sAML	Secondary AML
SAP	Statistical Analysis Plan
SAS	Safety analysis set
SOP(s)	Standard Operating Procedure(s)
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TTCR	Time to complete remission
TTR	Time to remission
UGT1A1	UDP (uridine diphosphate)-glucuronosyltransferase 1 family, polypeptide A1
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
WBC	White blood cell (count)
WHO	World Health Organization

6.4. Study Measures and Endpoints

6.4.1. Safety Measures and Endpoints

Safety will be evaluated by:

- Monitoring of adverse events (AEs), including determination of DLTs, serious adverse events (SAEs), and AEs leading to discontinuation. The severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
- Monitoring of safety laboratory parameters, physical examination findings, vital signs, 12-lead ECGs, evaluation of left ventricular ejection fraction (LVEF), and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

6.4.2. Pharmacokinetic and Pharmacodynamic Measures and Endpoints

The PK and PD profile of AG-221 will be evaluated by:

- Serial blood sampling at specified time points for determination of plasma concentration-time profiles and PK parameters of AG-221 and its metabolite AGI-16903.
- Urine sampling at specified time points for determination of concentrations of AG-221 and its metabolite AGI-16903 (dose escalation and Part 1 Expansion subjects only).
- Blood, bone marrow, and urine sampling at specified time points for determination of 2-HG levels to characterize the PD effects of AG-221.

6.4.3. Clinical Activity Measures and Endpoints

6.4.3.1. Phase 1 (Dose Escalation and Part 1 Expansion)

Clinical activity of AG-221 will be evaluated by:

- Serial blood and bone marrow sampling to determine response to treatment based on modified International Working Group (IWG) Response Criteria in AML (Cheson, et al. 2003) and in MDS (Cheson, et al. 2006) or other appropriate response criteria for the malignancy under study. Response for all subjects will be assessed by the site Investigators.

6.4.3.2. Phase 2

Eligibility, treatment decisions, and response to treatment will be determined by the Investigators based on modified International Working Group (IWG) response criteria (Table 7 and Table 8). Response will be also be assessed retrospectively by an Independent Response Adjudication Committee (IRAC).

- Other measures of clinical activity will be evaluated for subjects in this phase, including summaries of hematological recovery, including changes in platelets, hemoglobin, neutrophils, transfusion requirements, and infection rates.

6.4.4. Exploratory Endpoints

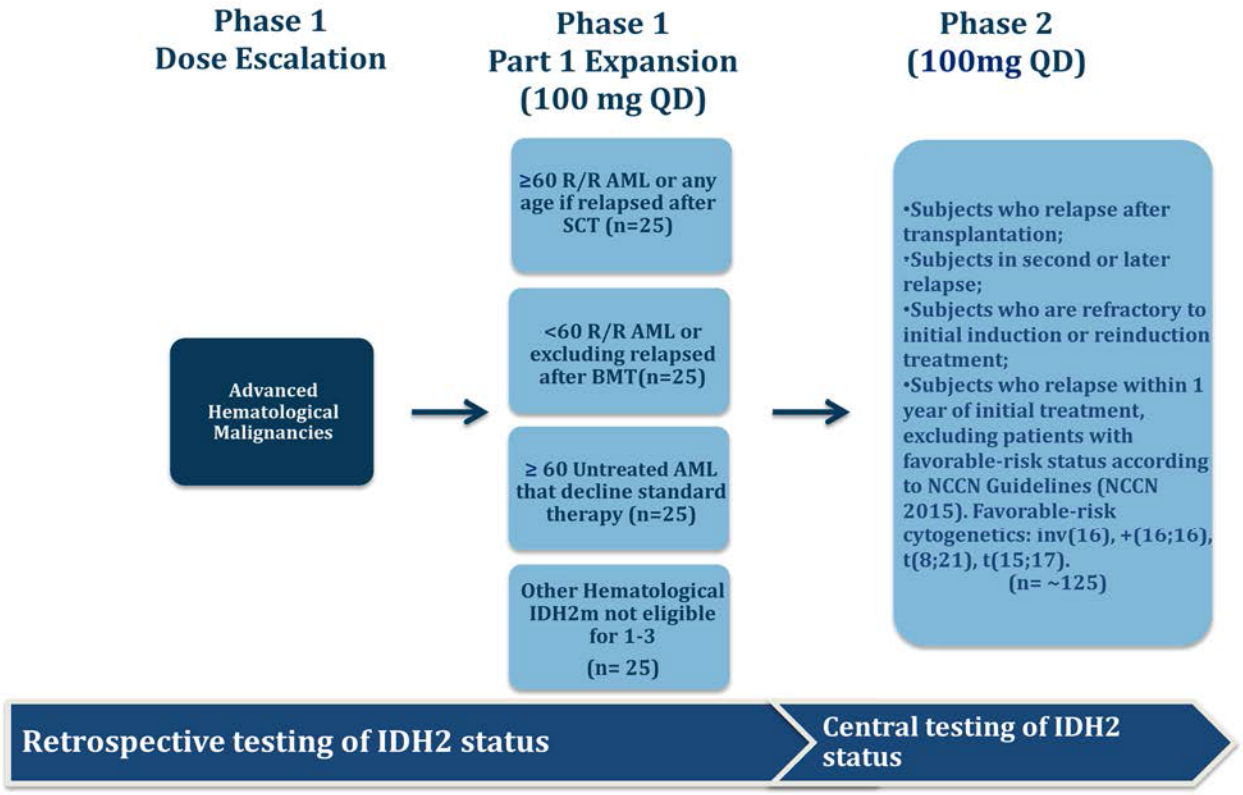
- [redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 1/2, multicenter, open-label, 3-part (Phase 1 dose escalation, Phase 1 Part 1 Expansion, and Phase 2), safety, PK/PD, and clinical activity evaluation of orally administered AG-221 in subjects with advanced hematologic malignancies that harbor an IDH2 mutation. The study includes a dose escalation phase to determine MTD /MAD and/or RP2D, an expansion phase (Part 1) to further evaluate the safety, tolerability, and clinical activity of AG-221, and a Phase 2 to assess the clinical efficacy of AG-221 at the RP2D and to further evaluate safety in subjects with refractory and relapsed AML carrying an IDH2 mutation.

Figure 6: Study Diagram



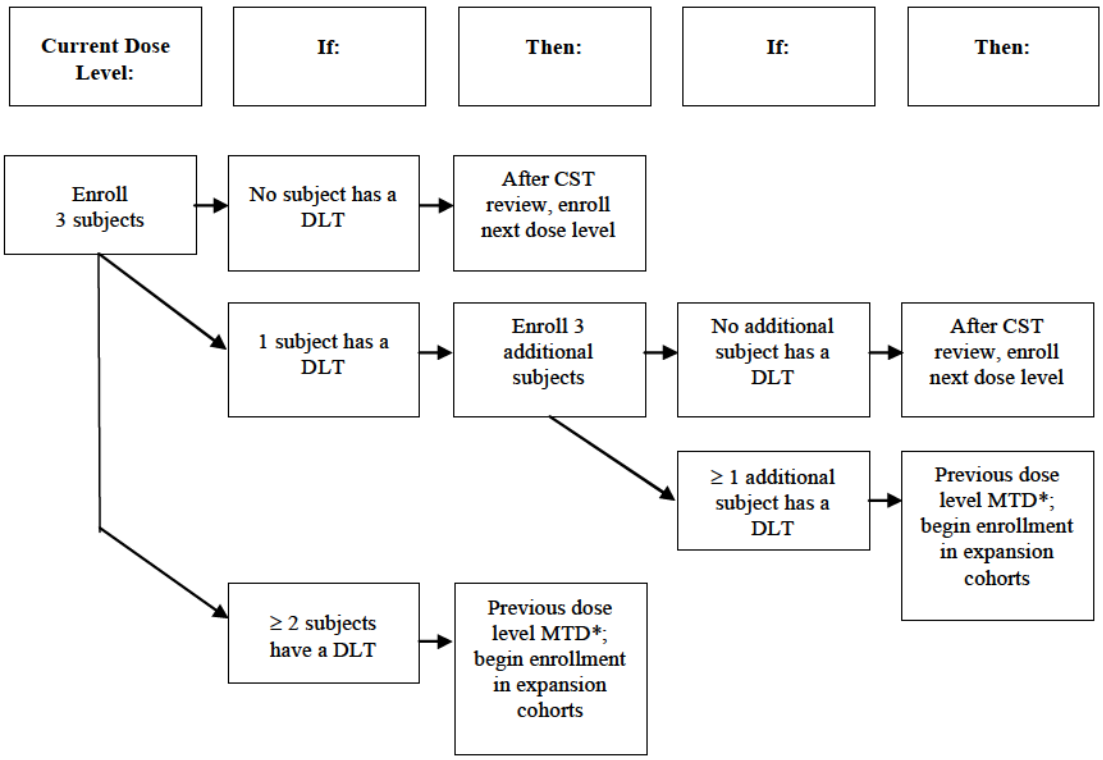
Note: Part 1 Expansion and Phase 2 at 100mg QD will proceed in parallel and as soon as this dose is declared safe during the dose escalation portion of the study.

7.1.1. Overview of the Phase 1/Dose Escalation Phase

A schematic of the dose escalation scheme is provided in Figure 7. The dose escalation phase will utilize a standard "3 + 3" design. During the dose escalation phase, consented eligible subjects will be enrolled into sequential cohorts of increasing doses of AG-221. Each dose cohort will plan to enroll a minimum of 3 subjects. The first 3 subjects in each cohort enrolled in the dose escalation phase will initially receive a single dose of AG-221 on Day -3 (i.e., 3 days prior to the start of daily dosing) to evaluate concentrations of AG-221, its metabolite AGI-16903, 2-HG and α-KG levels; safety also will be assessed. Daily dosing will begin on Cycle 1, Day 1

(C1D1). The initial dosing regimen was twice daily (approximately every 12 hours). Based on the emerging data, a once daily dosing schedule also has been implemented. Alternative dosing schedules (e.g., loading dose followed by once daily dosing) may continue to be explored in the dose escalation and expansion phases as agreed upon by the Clinical Study Team. 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, for a maximum of 5 subjects per cohort, with approval of the Medical Monitor. For these additional subjects, the Day -3 PK/PD assessments are optional following discussion with the Medical Monitor.

Figure 7: Dose Escalation Scheme



*If only 3 subjects were enrolled at the MTD level, an additional 3 subjects will be enrolled to confirm that <2 of 6 subjects experiences a DLT at this dose.
Note: CST = Clinical Study Team; DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Candidates for the dose-escalation phase of the study are adult subjects, 18 years of age or older, with:

- Diagnosis of AML according to WHO criteria (Appendix 15.1);
    - Disease refractory or relapsed (defined as the reappearance of > 5% blasts in the bone marrow, see Table 7 and Table 8) or
    - Untreated AML, ≥60 years of age and not candidates for standard therapy due to age, performance status, and/or adverse risk factors, according to the treating physician and with approval of the Medical Monitor;
- Diagnosis of Myelodysplastic syndrome with refractory anemia with excess blasts (subtype RAEB-1 or RAEB-2), or considered high-risk by the Revised International

Prognostic Scoring System (IPSS-R) (Appendix 15.3) (Greenberg, et al. 2012), that is recurrent or refractory, or the subject is intolerant to established therapy known to provide clinical benefit for their condition (i.e., subjects must not be candidates for regimens known to provide clinical benefit), according to the treating physician and with approval of the Medical Monitor.Subjects with other relapsed and/or primary refractory hematologic cancers, for example chronic myelomonocytic leukemia (CMML), who fulfill the inclusion/exclusion criteria may be considered on a case-by case basis, with approval of the Medical Monitor.

Confirmation of the primary malignancy is required. Subjects in the dose escalation phase are required to have IDH2 gene-mutated disease, documented by local site testing. Retrospective gene mutation analysis will be conducted at a central laboratory to support contemporaneous companion diagnostic development.

The safety of dosing will be evaluated by the Clinical Study Team, which is comprised of the Sponsor designee (Responsible Medical Officer), Study Medical Monitor, and Investigators. The Clinical Study Team will review the emerging safety data from each cohort to determine if dose escalation will occur. If, after the third subject completes the 28-day DLT evaluation period (i.e., Cycle 1), no DLTs are observed (see Section 9.7.1.1), the study will proceed with dose escalation to the next cohort following a review by the Clinical Study Team. 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, dose escalation may continue to the next cohort following review by the Clinical Study Team. If 2 or more subjects in a cohort experience DLTs during the first cycle, dose escalation will be halted and the next lower dose level will be declared the MTD. If the MTD cohort included only 3 subjects, an additional 3 subjects will be enrolled at that dose level to confirm that <2 of 6 subjects experience a DLT at that dose. Alternatively, a dose level intermediate between the non-tolerated dose level and the previously tolerated dose level may be explored and declared the MTD if <2 out of 6 subjects experience a DLT at that dose.

Note that if a given cohort initially enrolled 4 or 5 subjects (i.e., 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.

Toxicity severity will be graded according to the NCI CTCAE Version 4.03. A DLT is defined as outlined below:

Non-hematologic:

- All clinically significant non-hematologic toxicities CTCAE ≥ 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× upper limit of normal (ULN) may be considered a DLT.

Hematologic:

- Prolonged myelosuppression, defined as persistence of ≥ Grade 3 neutropenia or thrombocytopenia (by NCI CTCAE, version 4.03, leukemia-specific criteria, i.e., marrow cellularity <5% on Day 28 or later from the start of study drug without evidence of leukemia) at least 42 days after the initiation of Cycle 1 therapy. Leukemia-specific grading should be used for cytopenias (based on percentage decrease from baseline: 50 to 75% = Grade 3, >75% = Grade 4).

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-221 will be considered relevant to determining DLTs and will be reviewed by the Clinical Study Team.

The Clinical Study Team also will review any other emergent toxicities that are not explicitly defined by the DLT criteria to determine if any warrant a DLT designation.

Increases in the dose of AG-221 for each cohort will be guided by an accelerated titration design, where the dose will be doubled (100% increase) from one cohort to the next until CTCAE Grade 2 or greater AG-221-related toxicity is observed in any subject within the cohort. Following evaluation of the event(s) by the Clinical Study Team, subsequent increases in dose will be 50% or less until the MTD is determined. The absolute percent increase in the dose will be determined by the Clinical Study Team predicated on the type and severity of any toxicity seen in the prior dose cohorts (but will never exceed 100%). The MTD is the highest dose that causes DLTs in <2 of 6 subjects.

To optimize the number of subjects treated at a potentially clinically relevant dose, intra-subject dose escalation will be permitted with approval of the Medical Monitor (see Section 9.7.2).

Regularly scheduled teleconferences will serve as a forum for review of safety and other relevant data by the Clinical Study Team. Decisions to escalate the dose will be documented along with a summary of the information supporting the decision.

The planned study drug doses for the dose escalation phase are summarized in Table 1. The starting dose for this study is 30 mg administered approximately every 12 hours, based on the results of GLP dose range-finding studies (see Section 5.2.2.5). Based on evaluation of the safety, tolerability, and PK/PD data of the previous dose levels, it may also be decided that escalation will take place at an intermediate dose level not specified in the tables below. The maximum administered dose of AG-221 to be administered in this portion of the trial is 650 mg administered orally once a day. Enrollment in the dose escalation phase of this trial is complete, and no additional subjects will be enrolled.

Table 1: Planned Dose Escalation Scheme

BID Schedule AG-221 Dose (mg)	QD Schedule AG-221 Dose (mg)
30[1]	Not evaluated
50	50
75	75
100	100
150	150
Not evaluated	200
Not evaluated	300
Not evaluated	450
Not evaluated	650
[1]Starting Dose	

The results of a completed Phase 1 food-effect study in healthy volunteers (AG221-C-002) indicate a mild or moderate food effect on AG-221 plasma PK at 100 mg single dose. The 90% CIs (confidence intervals) of LSM (least-squares means) for PK parameters under fed versus fasted conditions were above the 80.00-125.00% range for Cmax, and AUC. There was an approximately 50% increase in AUC and a 64% increase in Cmax when AG-221 was administered under fed conditions compared with fasted conditions. Based on this, the effect of food and fasting on AG-221 exposure is being further evaluated in the dose escalation portion of this study. Specifically, AG-221 dosing without food restrictions will be conducted in 4 subjects at doses of 200 and 300 mg for 15 days of treatment (through C1D15) with the final formulation. Depending on these results, subjects in the Phase 2 portion of the trial may be dosed without food restriction.

7.1.2. Overview of the Phase 1/Part 1 Expansion

A dose of 100 mg QD has been selected for initial evaluation in Part 1 Expansion (see Section 7.3.2.). Different dosing regimens may be explored within the expansion phase of the study if warranted based on the emerging clinical safety, PK, PD and clinical activity data. During the expansion phase, safety, PK/PD, and preliminary clinical activity data will be reviewed by the Clinical Study Team every 8 weeks.

Part 1 Expansion phase will enroll approximately a minimum of 100 subjects divided into 4 non-randomized arms of approximately a minimum of 25 subjects per arm with IDH2-mutated hematologic malignancies as follows:

- Arm 1: Relapsed or refractory AML (Table 7 and Table 8) and age ≥60 years, or any subject with AML regardless of age who has relapsed following a BMT.
- Arm 2: Relapsed or refractory AML (Table 7 and Table 8) and age <60 years, excluding subjects with AML who have relapsed following a BMT.
- Arm 3: Untreated AML and age ≥60 years that decline standard of care chemotherapy.
- Arm 4: IDH2-mutated advanced hematologic malignancies not eligible for Arms 1 to 3.

As in the dose escalation phase, subjects in Part 1 Expansion are required to have IDH2 gene-mutated disease documented by local site testing with retrospective gene mutation analysis conducted at the central laboratory.

7.1.3. Overview of Phase 2

Based on continued ongoing demonstration of safety and clinical activity in the dose escalation portion of the study, the Phase 2 portion of the trial will further establish the clinical activity and safety profile of AG-221 in subjects with relapsed or refractory AML that harbor an IDH2 mutation .

The Phase 2 portion of the trial will enroll approximately 125 subjects with IDH2-mutated relapsed or refractory AML defined as follows (Table 7 and Table 8):

- Subjects who relapse after allogeneic transplantation
- Subjects in second or later relapse
- Subjects who are refractory to initial induction or re-induction treatment

Subjects who relapse within 1 year of initial treatment, excluding patients with favorable-risk status according to NCCN Guidelines (NCCN 2015). Favorable-risk cytogenetics: inv(16), t(16;16), t(8;21), t(15;17)The Phase 2 portion of the trial will be used to confirm the safety and clinical activity of AG-221 and to explore the relationship with PK/PD and IDH2 mutations for the treatment of subjects with relapsed or refractory AML that harbor an IDH2 mutation.

The starting dose of AG-221 recommended for evaluation for the Phase 2 portion of the trial is 100 mg QD. This is based on the safety, PK, pharmacodynamics and clinical activity of AG-221 observed to date in AG221-C-001. Evaluation of pharmacodynamic response demonstrated sustained reduction in 2-HG plasma levels by Day 1 of Cycle 2 and up to 98% inhibition in most subjects with R140Q mutation at all doses. Increasing dose is associated with higher exposure and inhibition of 2-HG in subjects with R172K mutation. Importantly, preliminary efficacy data of the 44 subjects treated at 100 mg QD has shown an overall response rate of 36.4%. Thus a dose of 100 mg should adequately achieve inhibition of 2-HG in subjects with either R140Q or R172K mutation. Moreover, the safety profile at 100 mg, including ≥ Grade 3, is consistent with that of lower doses.

Subjects in the Phase 2 portion of the trial are required to have IDH2- mutation tested centrally in samples of bone marrow aspirate **and/or** peripheral blood, and confirmed positive in bone marrow aspirate **and/or** peripheral blood during screening prior to study treatment.

The purpose of this phase is to provide an assessment of its antitumor activity in subjects with AML and characterize the safety and tolerability profile.

7.1.4. General Conduct

This is a multicenter study.

Approximately minimum of 291 subjects in total is planned to be enrolled in the study (i.e., in the dose escalation, Part 1 Expansion, and Phase 2).

Assuming that identification of the MTD requires the evaluation of 13 dose levels/schedules of AG-221 with up to 5 subjects per dose level, with the exception of the MTD, which requires 6 subjects, then 66 subjects will be enrolled during the dose escalation part of the study. Additional subjects may be needed for cohort expansion during dose escalation, for the replacement of subjects who are not evaluable for PK/PD, safety or clinical activity, or for evaluation of alternative dosing regimens other than the planned escalation scheme or the MTD, to optimize the RP2D and regimen(s).

As of April 2015, 5 dose levels (ranging from 30 mg to 150 mg) have been evaluated in the BID schedule and 8 dose levels (ranging from 50 mg to 650 mg) have been evaluated in the QD schedule.

Four cohorts of a minimum of 25 additional subjects in specific hematologic malignancy subsets (total of a minimum of 100 subjects) will be enrolled in Part 1 Expansion and 1 cohort of 125 subjects with relapsed or refractory AML will be enrolled in Phase 2. Additional subjects may be needed for the expansion phase for the replacement of subjects who are not evaluable for PK/PD, safety or clinical activity, or for evaluation of alternative dosing regimens.

The final total sample size may be adjusted according to the observed toxicity rate, and number of subjects enrolled for expanded evaluation.

Schedule of assessments for the study are provided in Table 2 through Table 5.

Screening Procedures

Following informed consent, all subjects will undergo screening procedures within 28 days prior to C1D1 to determine eligibility. All subjects are required to have confirmation of positive IDH2-mutated disease from a bone marrow aspirate and peripheral blood (report collected as a source document). For subjects in the dose escalation phase and Part 1 Expansion, documentation can be based on local site testing with central laboratory testing performed retrospectively.

Note: Subjects in the Phase 2 portion of the trial are required to have IDH2- mutation tested centrally in samples of bone marrow aspirate **and/or** peripheral blood, and confirmed positive in bone marrow aspirate **and/or** peripheral blood during screening prior to study treatment.

Additional screening procedures include collection of medical, surgical, and medication history; a buccal swab for germ-line mutation analysis; complete physical examination; vital signs; ECOG PS; 12-lead ECG; evaluation of LVEF; clinical laboratory assessments (hematology, chemistry, coagulation, and serum pregnancy test); bone marrow biopsy and/or aspirate; and blood for 2-HG, α-KG measurements, and determination of UGT1A1 mutation status. In addition, subjects in the dose escalation phase and Part 1 Expansion will have urine obtained for 2-HG and α-KG measurements and blood samples for cholesterol and 4β-OH-cholesterol levels during screening.

Pharmacokinetic/Pharmacodynamic and ECG Assessments

Phase 1/Dose Escalation

Three days prior to starting daily dosing of AG-221 (Day -3), the first 3 subjects in each cohort in the dose escalation phase and the first 15 subjects enrolled in each arm in Part 1 Expansion (unless approved by the Medical Monitor to omit the assessment) will receive a single dose of AG-221 in clinic and have serial blood and urine samples obtained for determination of blood/plasma and urine concentrations of AG-221, it's metabolite AGI-16903, 2-HG, and α-KG. A full 72-hour PK/PD profile will be obtained: subjects will be required to remain at the study site for 10 hours on Day -3 and return on Days -2, -1, and 1 for 24-, 48-, and 72-hour samples, respectively. During the in-clinic period on Day -3, clinical observation and serial 12-lead ECGs and vital signs assessments will be conducted over an 8-hour period after the first dose.

Daily treatment with AG-221 will begin on C1D1. Subjects in the dose escalation phase and Part 1 Expansion who did not receive the Day -3 dose of AG-221 are to remain in clinic for 8 hours after the C1D1 dose for clinical observation, serial 12-lead ECGs, and vital signs assessments.

After 12 months, subjects in the dose Phase 1 dose escalation will no longer undergo PK assessments, but bone marrow biopsy and/or aspirates as well as peripheral blood samples will still be collected for evaluation of disease, including exploratory biomarkers.

Phase 1/Part 1 Expansion

Subjects in the dose escalation phase and Part 1 Expansion will undergo PK/PD assessments over a 10-hour period on C1D15, C2D1, and C4D1. Predose blood samples (trough) will be obtained on C1D1 (for subjects who did not undergo the Day -3 assessments), C1D8, C1D22, C2D15, C3D1, C3D15, C5D1, and Day 1 of all cycles thereafter for determination of AG-221, and 2-HG, and α-KG concentrations. These subjects will have urine collected for PK/PD evaluation at screening; prior to dosing on C1D15, C2D1 and Day 1 of all cycles through cycle 12; and at the End of Treatment visit. Available bone marrow biopsy samples also will be assessed for 2-HG and α-KG levels.

After 12 months, subjects in the Phase 1 Part 1 Expansion will no longer undergo PK assessments, but bone marrow biopsy and/or aspirates as well as peripheral blood samples will still be collected for evaluation of disease, including exploratory biomarkers.

Phase 2

The Day -3 single dose and associated PK/PD assessments are not required for subjects enrolled in The Phase 2 portion of the trial; daily treatment with AG-221 will begin on C1D1. Subjects in The Phase 2 portion of the trial will have more limited PK/PD assessments conducted and will undergo time-matched triplicate ECGs. Available bone marrow samples will be assessed for 2-HG and α-KG levels.

For subjects in the Phase 2 portion of the trial, blood will be drawn for PK/PD assessment on Day 1 of Cycles 1 and 2 at the following time points: predose (within 30 minutes) and 2, 4, 6, and 8 hours (±10 minutes) post-dose. Additional blood samples for PK/PD assessments will be drawn predose (within 30 minutes) on Day 2 of Cycle 1, Day 2 of Cycle 2, Day 1 of Cycle 3, and at the End of Treatment visit.

Time-matched 12-lead ECGs will be conducted in triplicate on Day 1 of Cycles 1 and 2 at the following time points: predose (within 30 minutes) and 2, 4, and 6 hours post-dose (±15 minutes); a triplicate ECG is also to be obtained at the End of Treatment visit. When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample (within 10 minutes). Single 12-lead ECGs will also be conducted on Day 1 of every cycle beginning with Cycle 3 and at the Follow-up visit.

Other Safety Assessments

All subjects will undergo safety assessments during the treatment period to include physical examination, vital signs, ECOG PS, 12-lead ECGs, evaluation of LVEF, and clinical laboratory assessments (hematology, chemistry, coagulation, and pregnancy testing).

Clinical Activity Assessments

Phase 1 (Dose Escalation and Part 1 Expansion):

Subjects in the dose escalation phase and Part 1 Expansion will have the extent of their disease assessed, including bone marrow biopsies and/or aspirates, and peripheral blood, at screening, on C1D15, C2D1 and C3D1, and every 28 days (peripheral blood only) or every 56 days (bone marrow biopsies and/or aspirates and peripheral blood) thereafter while on study drug treatment, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected.

After at least 12 months, subjects in the dose escalation phase and Part 1 Expansion may have the extent of their disease assessed, including bone marrow biopsy, aspirates or peripheral blood based on their response to treatment.

Response to treatment and treatment decisions in all subjects will be determined by the Investigators based on modified International Working Group (IWG) response criteria or other appropriate response criteria for the malignancy under study (Section 10.8).

Phase 2:

For subjects enrolled in the Phase 2 portion of the trial extent of disease, including bone marrow biopsies and/or aspirates and peripheral blood, will be assessed at Screening, on C2D1, every 28 days thereafter through 12 months, and every 56 days thereafter while on study drug treatment, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected.

After at least 12 months, subjects in the Phase 2 portion of the trial may have the extent of their disease assessed, including bone marrow biopsy, aspirates or peripheral blood based on their response to treatment.

Eligibility, treatment decisions, and response to treatment will be determined by the Investigators based on modified International Working Group (IWG) response criteria (Table 7 and Table 8). Response will be also be assessed retrospectively by an Independent Response Adjudication Committee (IRAC).

End of Treatment and Follow-up

Subjects may continue treatment with AG-221 until disease progression or development of unacceptable toxicity. Subjects who experience disease progression per the applicable response criteria (Section 10.8) who are, in the opinion of the Investigator, benefiting from treatment may be allowed to continue on study drug with approval of the Medical Monitor.

All subjects are to undergo an end of treatment assessment (within approximately 5 days of the last dose of study drug); in addition, a follow-up safety assessment is to be scheduled 28 days after the last dose. Furthermore, all subjects will be followed monthly for disease status, overall survival, and initiation of non-study anti-neoplastic therapy until death, withdrawal of consent, or the end of the study, whichever occurs first.

Subjects who achieve an adequate response to treatment with AG-221 and meet other criteria required to undergo HSCT may proceed to HSCT after discontinuation of study therapy. Those subjects will be followed on study for outcome until disease relapse or end of study to support the overall clinical benefit of AG-221 in this setting.

Subjects who relapse following HSCT may be eligible to restart treatment with AG-221 with Medical Monitor approval and at the discretion of the Investigator, if they have confirmed recurrent IDH2 mutant positive disease, no cancer treatment was administered since the last dose of AG-221 (with the exception of anti-neoplastic therapies used in the course of HSCT such as conditioning regimen or induction-type regimen and anti-GVHD prophylaxis [i.e., methotrexate]), the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume AG-221 therapy at the same dose and schedule at the time of discontinuation of study drug.

All subjects are to be followed for survival status follow up every 3 months until death, withdrawal of consent, or end of study for survival. Serious AEs considered related to study drug should continue to be followed until death, withdrawal of consent, or the end of the study as per Section 11.2.

End of Study:

The End of Study is defined as either the date of the last visit of the last subject to complete the study, 3 years after the first dose of the last subject enrolled into Phase 2, or the date of receipt of the last data point from the last subject that is required for primary and secondary analysis, as pre-specified in the protocol, whichever is the later date.

[redacted]

[redacted]

7.4. Criteria for Study Termination

This study may be prematurely terminated, if in the opinion of the Sponsor, there is sufficiently reasonable cause. In the event of such action, written notification documenting the reason for study termination will be provided to each Investigator.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Failure to enter subjects at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Plans to modify, suspend, or discontinue the development of the study drug.
- Other administrative reasons.

Should the study be closed prematurely, all study materials must be returned to the Sponsor or Sponsor's designee. See Section 8.5 for specific requirements for subject termination from the study.

8. STUDY POPULATION

8.1. Number of Subjects

Approximately minimum of 291 subjects in total is planned to be enrolled in the study (i.e., in the dose escalation, Part 1 Expansion, and Phase 2). Assuming that 50% of subjects will not meet inclusion and/or exclusion criteria, i.e., are screen failures, approximately a minimum of 582 subjects will need to be screened to enroll a minimum of 291. Reasons for screen failure will be captured, including tumor samples obtained at screening that are IDH2 wild-type on local testing; note that tumor samples from these subjects also should be submitted for central evaluation.

Assuming that identification of the MTD requires the evaluation of 13 dose levels/schedules of AG-221, and requires the evaluation of up to 5 subjects per dose level with the exception of the MTD which requires 6 subjects, then 66 subjects will be enrolled during the dose escalation part of the study. Additional subjects may be needed for cohort expansion during dose escalation, for the replacement of subjects who are not evaluable for PK/PD, safety or clinical activity, or for evaluation of alternative dosing regimens other than the planned escalation scheme or the MTD, to optimize the RP2D and regimen(s).

As of April 2015, 5 dose levels (ranging from 30 mg to 150 mg) have been evaluated in the BID schedule and 8 dose levels (ranging from 50 mg to 650 mg) have been evaluated in the QD schedule.

Four cohorts of approximately a minimum of 25 additional subjects in specific hematologic malignancy subsets (see Section 7.1.2) (total of approximately a minimum of 100 subjects) will be enrolled in Part 1 Expansion of the study and 1 cohort of 125 subjects with relapsed or refractory AML will be enrolled in the Phase 2 portion of the trial (see Section 7.1.3). Additional subjects may be needed for the replacement of subjects who are not evaluable for PK/PD, safety or clinical activity, or for evaluation of alternative dosing regimens.

The final total sample size may be adjusted according to the observed toxicity rate, and number of subjects enrolled for expanded evaluation.

8.2. Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled in the study:

1. Subject must be ≥18 years of age.
2. Subjects must have an advanced hematologic malignancy including:

   Dose escalation:

   Phase 1/ Dose escalation:

   - Diagnosis of AML according to World Health Organization (WHO) criteria (Appendix 15.1);
     - Disease refractory or relapsed (defined as the reappearance of > 5% blasts in the bone marrow, see Table 7 and Table 8).

- Untreated AML, ≥60 years of age and are not candidates for standard therapy due to age, performance status, and/or adverse risk factors, according to the treating physician and with approval of the Medical Monitor;

- Diagnosis of MDS according to WHO classification (Appendix 15.2) with refractory anemia with excess blasts (subtype RAEB-1 or RAEB-2), or considered high-risk by the IPSS-R (Appendix 15.3) (Greenberg, et al. 2012), that is recurrent or refractory, or the subject is intolerant to established therapy known to provide clinical benefit for their condition (i.e., subjects must not be candidates for regimens known to provide clinical benefit), according to the treating physician and with approval of the Medical Monitor.

  (Subjects with other relapsed and/or primary refractory hematologic cancers, for example CMML, who fulfill the inclusion/excluding criteria may be considered on a case-by case basis, with approval of the Medical Monitor.)

Phase 1/Part 1 Expansion:

- Arm 1: Relapsed or refractory AML (Table 7 and Table 8) and age ≥60 years, or any subject with AML regardless of age who has relapsed following a BMT.
- Arm 2: Relapsed or refractory AML (Table 7 and Table 8) and age <60 years, excluding subjects with AML who have relapsed following a BMT.
- Arm 3: Untreated AML and age ≥60 years that decline standard of care chemotherapy.
- Arm 4: IDH2-mutated advanced hematologic malignancies not eligible for Arms 1 to 3.

Phase 2:

- Diagnosis of AML according to World Health Organization (WHO) criteria (Appendix 15.1) and disease relapsed or refractory as defined by (Table 7 and Table 8):
  - Subjects who relapse after allogeneic transplantation;
  - Subjects in second or later relapse;
  - Subjects who are refractory to initial induction or re-induction treatment;

3. Subjects who relapse within 1 year of initial treatment, excluding patients with favorable-risk status according to NCCN Guidelines (NCCN 2015). Favorable-risk cytogenetics: inv(16), +(16;16), t(8;21), t(15;17).Subjects must have documented IDH2 gene-mutated disease:

   - For subjects in the dose escalation phase and Part 1 Expansion, IDH2 mutation may be based on local evaluation. (Centralized testing will be performed retrospectively.)
   - For subjects in the Phase 2 portion of the trial, central testing of IDH2 mutation of bone marrow aspirate **and/or** peripheral blood, is required during screening to confirm eligibility.

4. Subjects must be amenable to serial bone marrow sampling, peripheral blood sampling, and urine sampling during the study.
    - The diagnosis and evaluation of AML or MDS will be made by bone marrow aspiration and/or biopsy. If an aspirate is unobtainable (i.e., a "dry tap"), the diagnosis may be made from the core biopsy.
    - Screening bone marrow aspirate **and** peripheral blood samples are required all subjects. A bone marrow biopsy must be collected if adequate aspirate is not attainable unless:
        - A bone marrow aspirate and biopsy was performed as part of the standard of care within 28 days prior to the start of the study treatment; and
        - Slides of bone marrow aspirate, biopsy and stained peripheral blood smear are available for both local and central pathology reviewers; and
        - A bone marrow aspirate sample acquired within 28 days prior to the start of study treatment has been sent for cytogenetic analysis.
5. Subjects must be able to understand and willing to sign an informed consent. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent, if acceptable to and approved by the site and/or site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
6. Subjects must have ECOG PS of 0 to 2 (Appendix 15.5).
7. Platelet count ≥20,000/μL (transfusions to achieve this level are allowed). Subjects with a baseline platelet count of <20,000/μL due to underlying malignancy are eligible with Medical Monitor approval.
8. Subjects must have adequate hepatic function as evidenced by:
    - Serum total bilirubin ≤1.5 × upper limit of normal (ULN), unless considered due to Gilbert's disease, a gene mutation in UGT1A1, or leukemic organ involvement, following approval by the Medical Monitor;
    - AST, ALT and ALP ≤3.0 × ULN, unless considered due to leukemic organ involvement.
9. Subjects must have adequate renal function as evidenced by:
    - Serum creatinine ≤2.0 × ULN

      OR
    - Creatinine clearance >40 mL/min based on the Cockroft-Gault glomerular filtration rate (GFR) estimation:

      $$(140 - \text{Age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})/72 \times \text{serum creatinine}$$
10. Subjects must be recovered from any clinically relevant toxic effects of any prior surgery, radiotherapy, or other therapy intended for the treatment of cancer. (Subjects with residual Grade 1 toxicity, for example Grade 1 peripheral neuropathy or residual alopecia, are allowed with approval of the Medical Monitor.)

11. Female subjects of child-bearing potential must agree to undergo medically supervised pregnancy test prior to starting study drug. The first pregnancy test will be performed at screening (within 7 days prior to first study drug administration), and on the day of the first study drug administration and confirmed negative prior to dosing and Day 1 before dosing all subsequent cycles.
12. Female subjects with reproductive potential must have a negative serum pregnancy test within 7 days prior to the start of therapy. Subjects with reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy or tubal occlusion or who have not been naturally postmenopausal (i.e., who have not menstruated at all) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Females of reproductive potential as well as fertile men and their partners who are female of reproductive potential must agree to abstain from sexual intercourse or to use two highly effective forms of contraception from the time of giving informed consent, during the study and for 120 days (females and males) following the last dose of AG-221. A highly effective form of contraception is defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization.
13. Able to adhere to the study visit schedule (ie, clinic visits at the study sites are mandatory, unless noted otherwise for particular study visits) and other protocol requirements

8.3. Exclusion Criteria

Subjects who meet any of the following criteria will not be enrolled in the study:

1. Subjects who have undergone a hematopoietic stem cell transplant (HSCT) within 60 days of the first dose of AG-221, or subjects on immunosuppressive therapy post HSCT at the time of screening, or with clinically significant graft-versus-host disease (GVHD). (The use of a stable dose of oral steroids post HSCT and/or topical steroids for ongoing skin GVHD is permitted with Medical Monitor approval.)
2. Subjects who received systemic anticancer therapy or radiotherapy <14 days prior to their first day of study drug administration. (Hydroxyurea is allowed prior to enrollment and after the start of AG-221 for the control of peripheral leukemic blasts in subjects with leukocytosis (white blood cell [WBC] counts >30,000/μL).
3. Subjects who received a small molecule investigational agent <14 days prior to their first day of study drug administration. In addition, the first dose of AG-221 should not occur before a period ≥5 half-lives of the investigational agent has elapsed.
4. Subjects taking the following sensitive CYP substrate medications that have a narrow therapeutic range are excluded from the study unless they can be transferred to other medications within ≥5 half-lives prior to dosing: paclitaxel (CYP2C8) warfarin, phenytoin (CYP2C9), S-mephenytoin (CYP2C19), thioridazine (CYP2D6), theophylline and tizanidine (CYP1A2).

5. Subjects taking the P-gp and BCRP transporter-sensitive substrates digoxin and rosuvastatin should be excluded from the study unless they can be transferred to other medications within ≥5 half-lives prior to dosing.
6. Subjects for whom potentially curative anticancer therapy is available.
7. Subjects who are pregnant or lactating.
8. Subjects with an active severe infection that required anti-infective therapy or with an unexplained fever >38.5°C during screening visits or on their first day of study drug administration (at the discretion of the Investigator, subjects with tumor fever may be enrolled).
9. Subjects with known hypersensitivity to any of the components of AG-221.
10. Subjects with New York Heart Association (NYHA) Class III or IV congestive heart failure or LVEF <40% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan obtained within approximately 28 days of C1D1.
11. Subjects with a history of myocardial infarction within the last 6 months of screening.
12. Subjects with uncontrolled hypertension (systolic blood pressure [BP] >180 mmHg or diastolic BP >100 mmHg) at screening are excluded. Subjects requiring 2 or more medications to control hypertension are eligible with Medical Monitor approval.
13. Subjects with known unstable or uncontrolled angina pectoris.
14. Subjects with a known history of severe and/or uncontrolled ventricular arrhythmias.
15. Subjects with a QTcF (QT corrected based on Fridericia's equation) interval ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome) at screening. Subjects with bundle branch block and a prolonged QTc interval should be reviewed by the Medical Monitor for potential inclusion.
16. Subjects taking medications that are known to prolong the QT interval (see Section 9.12.3 unless they can be transferred to other medications within ≥5 half-lives prior to dosing.
17. Subjects with known infection with human immunodeficiency virus (HIV) or active hepatitis B or C.
18. Subjects with any other medical or psychological condition, deemed by the Investigator to be likely to interfere with a subject's ability to sign informed consent, cooperate, or participate in the study.
19. Subjects with known dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally.
20. Subjects with clinical symptoms suggesting active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid is only required if there is a clinical suspicion of CNS involvement by leukemia during screening.

21. Subjects with immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation.
22. In the Phase 2 portion of the trial only, subjects who have previously received treatment with an inhibitor of IDH.

8.4. Subject Identification and Registration

Subjects who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria (see Sections 8.2 and 8.3, respectively) have been satisfied and that the subject is eligible for participation in this clinical study. The Medical Monitor will confirm eligibility for all subjects prior to receipt of the first dose of AG-221.

Trial personnel will have access to Interactive Response Technology (IRT, including an Interactive Web Response System [IWRS]) to allocate subjects, to assign treatment to subject, and to manage the distribution of clinical supplies. Investigator or designated site staff will be assigned password protected, coded identification numbers that give them authorization to access the IRT system to enroll subjects.

8.5. Subject Withdrawal Criteria and Replacement of Subjects

Subjects have the right to withdraw from the study at any time for any reason.

Subjects may withdraw or be withdrawn from study treatment for any of the following reasons:

- Withdrawal of consent
- Experiences unacceptable toxicity
- Any medical condition, which, in the opinion of the Investigators, would put the subject at risk for continuing treatment
- Experiences disease progression (subjects who are, in the opinion of the Investigator, benefiting from treatment may be allowed to continue on study drug with approval of the Medical Monitor)
- Confirmed pregnancy (study therapy should be immediately interrupted based upon a positive urinary human chorionic gonadotropin (hCG), and permanently discontinued if confirmed by a serum β-hCG test)
- Development of an intercurrent medical condition that precludes further participation in the trial
- The Investigator removes the subject from the trial in the best interests of the subject
- Subject requires use of a prohibited concomitant medication (Section 9.12.3)
- Protocol violation: non-adherence to study drug regimen or protocol requirements
- Lost to follow-up
- Death

Discontinuation from study treatment should be considered distinct from discontinuation from the study.

All subjects discontinued from study treatment for any reason should undergo End of Treatment (EOT) procedures, and will have a follow-up visit as described in Section 10.1. All subjects discontinued from study treatment for any reason will be followed further for disease status, overall survival, and initiation of non-study anti-neoplastic therapy until death, withdrawal of consent, or the end of the study, whichever occurs first. Every attempt should be made to collect all data during the follow-up period unless subjects discontinue from the study.

Following discontinuation of study drug, all efforts will be made to complete and report the protocol-defined study observations as completely as possible and to determine the reason for withdrawal.

Once a subject has discontinued study drug (or for a subject in the expansion phase who underwent HSCT post-treatment and has subsequently relapsed and elects not to restart treatment), he or she will enter the follow-up phase for survival.

All subjects are to be followed for survival status follow up every 3 months until death, withdrawal of consent, or end of study for survival.

In the event a subject is withdrawn from study drug or the follow-up phase of the study, the Medical Monitor must be informed. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

When a subject discontinues study drug or withdraws from the study, the primary reason(s) for discontinuation or withdrawal must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report final study observations as thoroughly as possible.

All AEs should be followed until resolution or for a period of 28 days from the last dose of study drug, whichever is shorter. If the subject withdrew from treatment because of an AE, every effort must be made to perform protocol-specified safety follow up procedures.

Serious AEs considered related to study drug should continue to be followed until death, withdrawal of consent, or the end of the study as per Section 11.

In addition, all pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or partner of a male subject occurring within 120 days of the subject's last dose of study drug, are considered immediately reportable events (Section 11.3).

For the dose escalation phase, subjects who do not meet the minimum treatment and safety evaluation requirements for evaluation of DLT (Section 9.7.1) and who do not experience DLT will be replaced if the minimum of 3 evaluable subjects within a cohort has not been satisfied.

- If ≥2 subjects within a cohort experience a DLT, then the previous dose level will be declared the MTD. Alternatively, a dose level intermediate between the non-tolerated dose level and the previously tolerated dose level may be explored and declared the MTD if <2 out of 6 subjects experience a DLT at that dose.

Note that if a given cohort initially enrolled 4 or 5 subjects (i.e., 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.

Increases in the dose of AG-221 for each dose cohort will be guided by an accelerated titration design, where the dose will initially be doubled (100% increase; see Table 1) from one cohort to the next until NCI CTCAE Grade 2 or greater AG-221-related toxicity is observed in 1 subject within the cohort. Following evaluation of the event(s) by the Clinical Study Team, subsequent increases in dose will be 50% or less until the MTD is determined. The absolute percent increase in the dose will be determined by the Clinical Study Team predicated on the type and severity of any toxicity seen in the prior dose cohorts (but will never exceed 100%). Based on the emerging data, alternative dosing schedules may be explored as agreed upon by the Clinical Study Team.

The MTD is the highest dose that causes DLTs in <2 of 6 subjects.

If no DLTs are identified during the dose escalation phase, dose escalation may continue for 2 dose levels above the projected maximum clinically effective dose, as determined by an ongoing assessment of PK/PD and any observed clinical activity; this may occur in parallel with the expansion phase.

9.7.1.1. Dose-limiting Toxicity

Dose-limiting toxicities will be evaluated during Cycle 1 of treatment. Toxicities will be graded and documented according to the NCI CTCAE, Version 4.03 (see Appendix 15.7). A DLT is defined as outlined below:

Non-hematologic:

- All clinically significant non-hematologic toxicities CTCAE ≥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× upper limit of normal (ULN) may be considered a DLT.

Hematologic:

- Prolonged myelosuppression, defined as persistence of Grade ≥3 neutropenia or thrombocytopenia (by NCI CTCAE, version 4.03, leukemia-specific criteria, i.e., marrow cellularity <5% on Day 28 or later from the start of study drug without evidence of leukemia) at least 42 days after the initiation of Cycle 1 therapy. Leukemia-specific grading should be used for cytopenias (based on percentage decrease from baseline: 50 to 75% = Grade 3, >75% = Grade 4).

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-221 will be considered relevant to determining DLTs and will be reviewed by the Clinical Study Team.

The Clinical Study Team also will review any other emergent toxicities that are not explicitly defined by the DLT criteria to determine if any warrant a DLT designation.

9.7.2. Intra-subject Dose Modification Criteria

9.7.2.1. Dose Escalation Criteria

Intra-subject dose escalation is permitted for all subjects following Medical Monitor approval.

Phase 1 Dose Escalation

Subjects who are receiving a lower dose of AG-221 than has been evaluated and determined to be safe (i.e., following safety review of that cohort there are <2 of 6 [or 0 of 3] subjects with DLTs) may be escalated to the higher safe dose pending review with the Medical Monitor. There is no limit to the number of times the dose of AG-221 may be increased for a given subject following Medical Monitor approval.

Phase 1 Part 1 Expansion

Subjects may only be dose-escalated once from their starting dose for the following:

- suboptimal response after the first clinical response assessment or later
- evidence of relapse on AG-221 after a response either in the peripheral blood or bone marrow

Phase 2

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

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

If benefit is demonstrated with an increased level of dose, then that dose level should be maintained during the subsequent treatment cycles that are given. However, once increased, the AG-221 dose may be reduced if a certain level of toxicity (eg, Section 9.7.2.2) is observed and considered as possibly or probably related to AG-221 treatment. Once reduced, the AG-221 dose should not be re-escalated unless there is evidence of morphologic relapse or PD. Any subject who is unable to tolerate 50 mg QD of AG-221 should be discontinued from study treatment.

9.7.2.2. Dose Reduction Criteria

All effort must be made to dose study drug according to schedule without cycle delay, dose interruption and reduction. Subjects will be monitored for hematologic toxicity and non-

hematologic toxicity with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) used as a guide for the grading of severity.

Dose reductions to a dose approved by the Medical Monitor and/or interruption of dosing may be allowed in the event of toxicities that are assessed as possibly or probably related to treatment with AG-221 following discussion with the Medical Monitor. If the time required for recovery from toxicity, i.e., return to at least baseline levels, is more than 28 days (1 cycle), a subject's continuation in the study should be discussed with the Medical Monitor regarding the risks and benefits of continuation. The AG-221 can be dose reduced in multiples of 50 mg. For example, at a starting dose of 200 mg QD, dose reductions should occur to 150 mg QD then to 100 mg QD and then to 50 mg QD. Any subject who is unable to tolerate 50 mg QD of AG-221 should be discontinued from study treatment.

Escalation back to the starting dose and/or an intermediate dose may be permitted with Medical Monitor approval.

Subjects who experience persistent Grade ≥3 toxicity that are assessed as possibly or probably related to treatment with AG-221 who are, in the opinion of the Investigator, benefiting from treatment may be allowed to continue on study drug with approval of the Medical Monitor. If the time required for recovery from toxicity, i.e., return to at least baseline levels, is more than 28 days (1 cycle), a subject's continuation in the study should be discussed with the Medical Monitor regarding the risks and benefits of continuation.

9.7.3. Dose Discontinuation Criteria

Dosing for an individual subject will be discontinued permanently for any DLT unless the subject is benefitting from study drug treatment per the Investigator and with approval of the Medical Monitor; a dose reduction may be considered (Section 9.7.2). Other reasons for treatment termination are provided in Section 8.5.

9.8. Guidelines for Important Events

The following are guidelines for the management of adverse events of special interest based on the non-clinical and clinical safety findings to date.

9.8.1. Guidelines for Management of QT Prolongation

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

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

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medication with known QT prolonging effects.

- If no other cause is identified and the Investigator believes it is appropriate, particularly if QTc remains elevated (after above measures have been implemented, or as determined by the Investigator), 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-221 should be considered if held. ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTc reduction ≤ 480 msec.
    - If Grade 2 (QTcF > 480 and ≤ 500 msec), the dose of AG-221 may be reduced to a dose approved by the medical monitor without interruption of dosing. The AG-221 dose may be re-escalated to the prior dose in ≥ 14 days after QT prolongation has decreased to ≤ Grade 1.
        - If this is the second occurrence of QT prolongation, administration of AG-221 should continue at a reduced dose (ie, the dose may not be re-escalated).
    - If Grade 3 (QTcF > 500 msec), when QTc prolongation is first observed, hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be done. Dosing with 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-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-221 should be permanently discontinued.

9.8.2. IDH Differentiation Syndrome

Subjects treated with 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.

9.8.3. Leukocytosis

Initiation of treatment with the differentiating agents may lead to rapid WBC expansion not associated with infectious 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 3 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.

9.8.4. Gastrointestinal Disorders (Diarrhea, Nausea, Vomiting, Decreased Appetite, and Alterations in Taste)

Monitoring and timely management of gastrointestinal events, as appropriate, is critical in avoiding malnourishment and dehydration.

9.8.5. Tumor Lysis Syndrome

Tumor Lysis Syndrome can causes abnormalities in your blood such as higher than normal levels of potassium and phosphorus or low levels of calcium with elevation of uric acid levels (hyperuricaemia) and may affect kidney function. Monitoring electrolytes and kidney function is advised and subjects may need to be treated with additional fluids or other medications, as appropriate.

9.8.6. Increased blood bilirubin

AG-221 slows breakdown of bilirubin, causing blood bilirubin increased. Liver enzyme monitoring may be instituted. Elevated blood bilirubin may also cause skin yellowing.

9.9. Duration of Subject Participation

9.9.1. Treatment Duration

Subjects may continue treatment with AG-221 until disease progression, development of unacceptable toxicity or confirmed pregnancy. Subjects who experience disease progression per the applicable response criteria (Section 10.8) who are, in the opinion of the Investigator, benefiting from treatment may be allowed to continue on study drug with approval of the Medical Monitor.

All subjects are to undergo an end of treatment assessment (within approximately 5 days of the last dose of study drug); in addition, a follow-up safety assessment is to be scheduled 28 days after the last dose.

All subjects are to be followed for survival status follow up every 3 months until death, withdrawal of consent, or end of study for survival.

Subjects who achieve an adequate response to treatment with AG-221 and meet other criteria required to undergo HSCT may proceed to HSCT after discontinuation of study therapy. Those subjects will be followed on study for outcome until relapse or end of study to support the overall clinical benefit of AG-221 in this setting.

Subjects who relapsed after HSCT may be eligible to restart treatment with AG-221 with Medical Monitor approval and at the discretion of the Investigator, if they have confirmed recurrent IDH2 mutant positive disease, no cancer treatment was administered since the last dose of AG-221 (with the exception of anti-neoplastic therapies used in the course of HSCT such as conditioning regimen or induction-type regimen and anti-GVHD prophylaxis [i.e., methotrexate]), the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume AG-221 therapy at the same dose and schedule at the time of discontinuation of study drug.

All subjects, including subjects who relapse following HSCT and elect not to restart treatment, will be contacted monthly thereafter for assessment of survival status and anti-neoplastic therapies since discontinuation of study drug until death or end of study.

9.9.2. End of Study

The End of Study is defined as either the date of the last visit of the last subject to complete the study, 3 years after the first dose of the last subject enrolled into Phase 2, or the date of receipt of the last data point from the last subject that is required for primary and secondary analysis, as pre-specified in the protocol, whichever is the later date.

9.10. Treatment Compliance

Subjects will be dispensed the appropriate number of Sponsor-packaged, labeled bottle(s) for 28 days of dosing on Day 1 of each cycle; alternatively, subjects may be dispensed the appropriate number of bottle(s) needed until the next study visit. The subject will be asked to return all bottles and unused tablets (or empty bottles) on Day 1 of each cycle or at their next study visit for assessment of compliance with the dosing regimen and at EOT visit.

9.11. Study Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and return to Celgene or its designee (or disposal of the drug, if approved by Celgene). These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from Celgene. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and subject numbers. The Investigator(s) or designee(s) will verify the accuracy of the information on the form and access the IRT system to register the study medication received at the site.

The Sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

Study drug must not be used for any purpose other than the present study. Study drug which has been dispensed to a subject and returned unused must not be re-dispensed to a different subject.

Subjects will receive instructions for home administration of AG-221 along with a diary to record the date and time of each dose, as well as the number and strength (mg) of tablets taken.

All unused and used study drug will be retained at the site until they are inventoried by the study monitor. All used, unused or expired study drug will be returned to Celgene or its designee or if authorized, disposed of at the study site per the site's Standard Operating Procedures (SOPs) and documented. All material containing AG-221 will be treated and disposed of as hazardous waste in accordance with governing regulations.

9.12. Prior and Concomitant Medications and Treatments

10. STUDY ASSESSMENTS

10.1. Schedule of Events

Table 2 and Table 3 provide the schedules of assessments for subjects enrolled in Phase 1 and for subjects enrolled in the Phase 2 portion of the trial, respectively. Table 4 and Table 5 provide the Pharmacokinetic and Pharmacodynamic Sampling and Electrocardiogram Schedule for subjects enrolled in Phase 1 and for subjects enrolled in Phase 2, respectively.

After obtaining written informed consent, subjects will undergo screening evaluations. The screening visit is to be conducted within 28 days prior to C1D1. For subjects who receive a single dose of study drug on Day -3, all screening procedures should be complete prior to first study drug administration. Subjects are to attend study center visits as outlined in the schedules of assessments (Table 2 and Table 3). A detailed description of study assessments follows the tables.

For subjects in the Phase 2 portion of the trial, central testing of IDH2 mutation is required during screening to confirm eligibility and should be performed before all other assessments to diminish the number of invasive tests on subjects for whom eligibility may not be confirmed.

All study center visits will be conducted on an outpatient basis. Whenever possible, the study visit should occur on the scheduled visit day; a ±2-day window is allowed to accommodate subjects' schedules. The first 3 subjects in each cohort enrolled in the dose escalation phase of the study and the first 15 subjects in each arm of Part 1 Expansion (unless approved by the Medical Monitor to omit the assessment) will initially receive a single dose of AG-221 on Day -3. Following the Day -3 dose, subjects are required to remain at the study center for 10 hours for serial blood and urine samples and clinical observations and assessments; subjects are to return to the clinic on Days -2, -1 and 1 for 24-, 48- and 72-hour PK/PD assessments, respectively. The Day -3 dose and PK/PD assessments are not required for subjects in the Phase 2 portion of the trial.

Following the C1D1 dose of study treatment, subjects in the dose escalation phase and Part 1 Expansion who did not receive the Day -3 dose of AG-221 are required to remain at the study center for 8 hours for clinical observation and assessments.

Subjects in the dose escalation and Part 1 Expansion are to remain at the study center for 10 hours following the C1D15, C2D1 and C4D1 doses for PK/PD assessments. In addition, these subjects are required to receive their first daily dose of study drug in clinic in order to obtain predose (trough) samples on C1D1 (for subjects who did not undergo the Day -3 PK/PD assessments), C1D8, C1D22, C2D15, C3D1, C3D15, C5D1, and Day 1 of all cycles thereafter for determination of AG-221 and 2-HG concentrations.

After 12 months, subjects in the Phase 1 dose escalation will no longer undergo PK assessments, but bone marrow biopsy and/or aspirates as well as peripheral blood samples will still be collected for evaluation of disease, including exploratory biomarkers.

Subjects in the Phase 2 portion of the trial are to remain at the study center for at least 8 hours following the C1D1 and C2D1 doses for PK/PD and triplicate ECG assessments and are required to receive their first daily dose of study drug in clinic on C1D2, C2D2 and C3D1 in order to obtain predose (trough) samples.

An End of Treatment (EOT) visit will be conducted as soon as possible after discontinuing study treatment (within 5 days of last dose of study drug); in addition, subjects are to attend a Follow-up visit 28 days after the last dose of study drug for final assessments.

All subjects are to be followed for survival status follow up every 3 months until death, withdrawal of consent, or end of study for survival. Serious AEs considered related to study drug should continue to be followed until death, withdrawal of consent, or the end of the study as per Section 11.2.

Subjects who discontinue from study treatment and undergo HSCT will enter HSCT follow-up and are to be evaluated on study until relapse or end of study. Subjects who relapsed after HSCT may be eligible to restart treatment with AG-221 with Medical Monitor approval and at the discretion of the Investigator, if they have confirmed recurrent IDH2 mutant positive disease, no cancer treatment was administered since the last dose of AG-221 (with the exception of anti-neoplastic therapies used in the course of HSCT such as conditioning regimen or induction-type regimen and anti-GVHD prophylaxis [i.e., methotrexate]), the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume AG-221 therapy at the same dose and schedule at the time of discontinuation. These subjects will 're-enter' the study at Cycle 3 and have assessments conducted per that visit and beyond.

Table 2: Schedule of Assessments: Phase 1(Dose Escalation and Part 1 Expansion)

Visit/Cycle:	Scrn	Day -3[12]	Cycle 1				Cycle 2		Cycle 3[4] – Cycle 12		Cycle 13[31] and beyond	EOT[3]	Safety Follow-up Visit	Follow-up HSCT[4]	Survival Follow-up[5]
Study Day:	D -28		D1[2]	D8	D15[2]	D22	D1[2]	D15	D1[2]	D15	D1		28 days post Discon.	Every 28 Days	Every 28 Days
Informed Consent	X														
Review Entry Criteria	X														
Demographics	X														
Medical and Surgical History	X														
Medication History	X														
Complete Physical Exam	X											X			
Limited Physical Exam		X	X	X	X		X		X		X				
Height[6] and Weight	X	X	X		X		X		X		X	X			
ECOG PS	X	X	X		X		X		X		X	X	X		
Vital Signs[7]	X				X		X		X			X			
Serial Vital Signs[7,8]		X	X												
Single 12-lead ECG[9]		Please refer to Table 4													
Serial single 12-lead ECG[9]															
ECHO/MUGA for LVEF	X								X[10]			X[10]			
Gene Mutation Analysis[11]	X														
UGT1A1 Gene Testing	X														
Laboratory Evaluations:															
Hematology[12]	X	X	X	X	X	X	X	X	X	X	X	X		X[13]	
Serum Chemistry[14]	X	X	X	X	X	X	X	X	X	X	X	X			
Coagulation Studies[15]	X	X	X		X		X		X		X	X			
Fasting Lipid Panel[16]	X								X[16]		X	X			
Pregnancy Test[17]	X	X	X				X		X		X	X			
Bone Marrow Biopsy and Aspirate[18,19]	X				X		X		X		X	X		X[13]	

Visit/Cycle:	Scrn	Day -3[1,2]	Cycle 1				Cycle 2		Cycle 3[4] – Cycle 12		Cycle 13[31] and beyond	EOT[3]	Safety Follow-up Visit	Follow-up HSCT[4]	Survival Follow-up[5]
Study Day:	**D -28**		**D1[2]**	**D8**	**D15[2]**	**D22**	**D1[2]**	**D15**	**D1[2]**	**D15**	**D1**		**28 days post Discon.**	**Every 28 Days**	**Every 28 Days**
Peripheral blood for IDH2-mutated cells/leukemic blasts, plasma, and neutrophils[19]	X				X		X		X		X	X		X[13]	
Evaluate Extent of Disease and Response to Treatment[19,20]					X		X		X		X	X[21]	X	X[13]	
Transfusion Assessment[22]	X				X		X		X		X	X[21]	X	X[13]	
Single-dose Study Drug Administration[23,24]		X													
Study Drug Administration[24]			X	X	X	X	X	X	X	X	X[32]				
Compliance Assessment[25]							X		X		X	X			
PK/PD Assessments[26]		Please refer to Table 4													
Blood Sampling[26]															
Urine Sampling[26]															
Adverse Events	X	X	X	X	X	X	X	X	X	X	X[33]	X	X[27]		
Concomitant Medications / Procedures	X	X	X	X	X	X	X	X	X	X	X[33]	X	X		
Study Completion[28]													X		
Survival Status[29]													X	X	X
New Anti-neoplastic Therapy[30]													X	X	X

D = Day, Discon= discontinuation, EOT= End of Treatment, ECG = electrocardiogram, ECHO = echocardiography, ECOG = Eastern Cooperative Oncology Group, IWG = International Working Group, LVEF = left ventricular ejection fraction, MUGA = multiple gated acquisition, PD = pharmacodynamic, PK = pharmacokinetic, PS = performance status, Scrn = screening

Note: All cycles are 28 days in duration, there are no rest periods between cycles.

Note: Whenever possible, the study visit should occur on the scheduled visit day; a ±2-day window is allowed to accommodate subjects' schedules.

[1] Procedures listed on Day -3 are for the first 3 subjects enrolled in each cohort during the dose escalation phase of the study and for the first 15 subjects enrolled within each of the 4 arms of Part 1 Expansion unless approved by the Medical Monitor to omit the assessment.
[2] Subjects are to remain in the clinic for 8 or 10 hours after the first (daily) dose of study drug administration (Day -3 [10 hours] or C1D1 [8 hours] as applicable) for observation, serial 12-lead ECGs, serial vital signs (Day -3 or C1D1), and for PK/PD assessments (Day -3, C1D15, C2D1, and C4D1).
[3] Assessments to be conducted on the last day of study treatment (within 5 days of last dose of study drug).
[4] All subjects who undergo HSCT following discontinuation of AG-221 are to be followed after the last dose until relapse, start of new anti-neoplastic treatment, or end of study. Subjects who relapse and have recurrent IDH2-mutant positive disease may be eligible to restart treatment with AG-221 with Medical Monitor approval; these subjects will 're-enter' the study at Cycle 3 assessments. Subjects who relapse and elect not to restart treatment will enter the survival follow-up phase.
[5] Subject should be followed (either with in-person visit or contacted by phone) every 28 days to assess for survival status. All subjects are to be followed for survival status follow up every 3 months until death, withdrawal of consent, or end of study for survival.
[6] Height is to be obtained only at the screening assessment.
[7] Systolic and diastolic blood pressure (BP), heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is seated or supine.
[8] Serial vital signs are to be conducted predose and 30 ± 10 minutes and 2, 4, 6 and 8 hours (± 15 minutes) post dose following the morning administration of study drug (prior to performing serial ECG assessments).
[9] Refer to Table 4 for complete ECG assessment schedule, including timing of serial samples.
[10] Procedure is to be conducted on C3D1 and Day 1 every other cycle thereafter (e.g., C5D1, C7D1, etc), at the End of Treatment visit and at the Follow-up visit. The same procedure to evaluate LVEF should be conducted throughout the study.
[11] Gene mutation analysis for confirmation of IDH2-mutated disease from a bone marrow sample will be conducted on all subjects. For subjects in the dose escalation phase and Part 1 Expansion, the confirmation will be based on the local site's testing platform with central laboratory testing performed retrospectively. A separate tumor (blood and/or bone marrow) sample will be required for central laboratory biomarker analysis (see Section 10.5). A buccal swab for germ-line mutation analysis will be obtained at screening.
[12] Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, and blast count.
[13] If performed, the results and/or samples of hematological assessments, bone marrow biopsies and/or aspirates, peripheral blood for molecular and functional studies of blasts and neutrophils, and evaluation of the extent of disease and response to treatment will be collected and assessed as part of the study for subjects who undergo HSCT after discontinuation of AG-221. These subjects will be followed at least monthly for assessment of disease response until relapse of end of study.
[14] Sodium, potassium, chloride, calcium, magnesium, phosphorus, carbon dioxide (CO_2), bicarbonate (HCO_3), albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, and indirect bilirubin. In addition, creatine kinase, cardiac troponin, amylase, and lipase are to be obtained at screening, Day -3 (for subjects undergoing 72-hour PK/PD profile), on Day 1 of each treatment cycle, and at the End of Treatment visit.
[15] Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR).
[16] Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides. To be conducted at screening, every 6 cycles on treatment, and at the End of Treatment visit.
[17] A serum pregnancy test will be performed at screening (within 7 days prior to first study drug administration) and at the EOT. A urine pregnancy test must be conducted on the day of first study drug administration and confirmed negative prior dosing (Day -3 for subjects undergoing 72-hour PK/PD profile or on C1D1) and Day 1 of all subsequent cycles.

[18] Bone marrow aspirates and core sampling should be performed according to standard of care and analyzed at the local site's laboratory in accordance with the International Council for Standardization in Hematology (ICSH) Guidelines (Lee, et al. 2008) (see Section 10.7). Analyses should include cytogenetics and flow cytometry according to institutional standards and results should be recorded in the eCRFs.

[19] Assessment to be conducted on C1D15, C2D1 and C3D1; following C3D1 assessment, evaluation of disease response, including bone marrow assessment, will be conducted every 56 days during treatment through at least the Month 12 (see Section 10.8.1) while peripheral blood for plasma and IDH2-mutated cells, including leukemic blasts and neutrophils, will be conducted every 28 days during treatment through at least Month 12 (see Section 10.8.1), independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. After at least 12 months, subjects may have the extent of their disease assessed, including bone marrow biopsy, aspirates or peripheral blood based on their response to treatment.

[20] Subjects will have the extent of their disease assessed based on modified IWG criteria or other appropriate response criteria for the malignancy under study (see Section 10.8).

[21] Response to treatment is to be assessed at this visit if the subject discontinues treatment for reasons other than disease progression.

[22] Subjects are also to be evaluated for RBC and platelet transfusions (dates and units administered) and associated hemoglobin levels and/or platelet counts at each response assessment and as clinically indicated.

[23] 72-hour PK/PD assessments will be conducted for the first 3 subjects enrolled in each cohort during the dose escalation phase and the first 15 subjects enrolled in each arm in the expansion phase (unless approved by the Medical Monitor to omit the assessment) following a single dose of AG 221 administered on Day -3; these procedures are optional (based on Medical Monitor evaluation) for any additional subjects enrolled in a cohort during the dose escalation and Part 1 Expansion. All screening assessments must be completed prior to single dose administration on Day -3.

[24] The morning doses on Day -3, C1D1, C1D8, C1D15, C1D22, C2D15, C3D15, and Day 1 of all cycles after cycle 1 (C2D1, C3D1, etc.) are to occur in clinic to accommodate full PK/PD sampling (Day -3, C1D15, C2D1, and C4D1) and to allow for predose assessments (C1D1 [for subjects who did not undergo the Day -3 assessments], C1D8, C1D22, C2D15, C3D1, C3D15, C5D1 and Day 1 of all cycles thereafter) (see Table 4)

[25] Treatment compliance is to be assessed based on return of unused drug as well as subject diaries.

[26] Refer to Table 4 for complete serial PK/PD sampling schedule. See Section 10.11 for details on sampling for plasma cholesterol and 4β-OH-cholesterol levels, and Section 10.10 for details for urine and blood sampling for 2-HG and α-KG.

[27] Any serious adverse events (SAEs) that are assessed by the Investigator as possibly or probably related to study treatment that occur >28 days post-treatment also are to be reported.

[28] Subjects who do not go to HSCT are considered to have completed the study at the time of the Day +28 follow-up assessment; subjects who undergo HSCT after discontinuation of AG-221 remain on study until relapse, start of a new medication, or end of study. All subjects enter the survival follow-up phase after study completion.

[29] After the safety follow-up assessments, or for subjects who relapse after HSCT and elect not to restart treatment, subjects are to be followed every 28 days to assess survival status until death or end of study. After 12 month of survival status follow up, subjects are to be followed every 3 months until death or end of study.

[30] All new anti-neoplastic therapies administered after the last dose of AG-221 are to be captured for all subjects through end of study.

[31] Starting at Cycle 13, all assessments may be reduced to every 3 cycles unless otherwise indicated.

[32] Starting at Cycle 13, 3 Cycles of AG-221 should be dispensed.

[33] Adverse events and concomitant medication must still be captured every 28 days. On cycle Day 1 (every (28 days) when assessments are not performed documented phone contact is acceptable.

Table 3: Schedule of Assessments: Phase 2

Visit/Cycle:	Scrn	Cycle 1					Cycle 2			Cycle 3[4] – Cycle 12		Cycle 13 and beyond[29]	EOT[1]	Follow-up	Follow-up HSCT[2]	Survival Follow-up[3]
Study Day:	**D -28**	**D1[4]**	**D2**	**D8**	**D15**	**D22**	**D1[4]**	**D2**	**D15**	**D1**	**D15**	**D1**		**28 Days post Discon**	**Every 28 Days**	**Every 28 Days**
Informed Consent	X															
Review Entry Criteria	X															
Demographics	X															
Medical and Surgical History	X															
Medication History[5]	X															
Complete Physical Exam	X												X			
Limited Physical Exam		X		X	X		X			X		X				
Height[6] and Weight	X	X			X		X			X		X	X			
ECOG PS	X	X			X		X			X		X	X	X	X	
Vital Signs[7]	X				X		X			X			X		X	
Serial Vital Sign[7,8]		X														
Single 12-lead ECG[9]		Please refer to Table 5														
Serial Triplicate 12-lead ECGs[9]																
ECHO/MUGA for LVEF	X									X[10]			X			
Gene Mutation Analysis[11]	X															
UGT1A1 Gene Testing	X															
Laboratory Evaluations:																
Hematology[12]	X	X		X	X	X	X		X	X	X	X	X		X[13]	
Serum Chemistry[14]	X	X		X	X	X	X		X	X	X	X	X		X	
Coagulation Studies[15]	X	X			X		X			X		X	X		X	
Pregnancy Test[16]	X	X					X			X		X	X			
Bone Marrow Biopsy and Aspirate[17,18]	X						X			X		X	X		X[13]	

Visit/Cycle:	Scrn	Cycle 1					Cycle 2			Cycle 3[4] – Cycle 12		Cycle 13 and beyond[29]	EOT[1]	Follow-up	Follow-up HSCT[2]	Survival Follow-up[3]
Study Day:	**D -28**	**D1[4]**	**D2**	**D8**	**D15**	**D22**	**D1[4]**	**D2**	**D15**	**D1**	**D15**	**D1**		**28 Days post Discon**	**Every 28 Days**	**Every 28 Days**
Peripheral blood for molecular and functional studies of plasma, blasts and neutrophils[18]	X						X			X		X	X		X[13]	
Evaluate Extent of Disease and Response to Treatment[18,19]							X			X		X	X[20]		X[13]	
Transfusion Assessment[21]	X						X			X		X	X[20]		X[13]	
Study Drug Administration[22]		X	X	X	X	X	X	X	X	X	X	X[30]				
Compliance Assessment[23]							X			X		X	X			
PK/PD Assessment[24]		Please refer to Table 5														
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[31]	X	X[25]		
Concomitant Medications / Procedures	X	X	X	X	X	X	X	X	X	X	X	X[31]	X	X	X	
Study Completion[26]														X	X	X
Survival Status[27]														X	X	X
New Anti-neoplastic Therapy[28]														X	X	

D = Day, Discon= discontinuation, EOT=Endo of Treatment, ECG = electrocardiogram, ECHO = echocardiography, ECOG = Eastern Cooperative Oncology Group, HSCT = hematopoietic stem cell transplant, IWG = International Working Group, LVEF = left ventricular ejection fraction, MUGA = multiple gated acquisition, PD = pharmacodynamic, PK = pharmacokinetic, PS = performance status, Scrn = screening

Note: All cycles are 28 days in duration, there are no rest periods between cycles.

Note: Whenever possible, the study visit should occur on the scheduled visit day; a ±2-day window is allowed to accommodate subjects' schedules.

1. Assessments to be conducted on the last day of study treatment (within 5 days of last dose of study drug).
2. All subjects who undergo HSCT following discontinuation of AG-221 are to be followed after the last dose until relapse or end of study. Subjects who relapse and have recurrent IDH2-mutant positive disease may be eligible to restart treatment with AG-221 with Medical Monitor approval; these subjects will 're-enter' the study at Cycle 3 assessments. Subjects who relapse and elect not to restart treatment will enter the survival follow-up phase.
3. Subject should be followed (either with In-person visit or contacted by phone) every 28 days to assess for survival status. All subjects are to be followed for survival status follow up every 3 months until death, withdrawal of consent, or end of study for survival.
4. Subjects are to remain in the clinic for at least 8 hours after the C1D1 and C2D1 doses for clinical observation, serial triplicate ECGs, serial vital signs (C1D1 only) and PK/PD assessments.

[5] To include information on red blood cell (RBC) and platelet transfusions (dates and units administered) and associated hemoglobin levels and/or platelet counts for the 8-week period prior to C1D1.
[6] Height is to be obtained only at the screening assessment.
[7] Systolic and diastolic blood pressure (BP), heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is seated or supine.
[8] Serial vital signs are to be conducted predose and 30 ± 10 minutes and 2, 4, 6 and 8 hours (± 15 minutes) post dose following the morning administration of study drug (prior to performing serial ECG assessments).
[9] Refer to Table 5 for complete ECG assessment schedule, including timing of serial samples in Cycles 1 and 2.
[10] Procedure is to be conducted on C3D1 and Day 1 every other cycle thereafter (e.g., C5D1, C7D1, etc), at the End of Treatment visit and at the Follow-up visit. The same procedure to evaluate LVEF should be conducted throughout the study.
[11] Gene mutation analysis for confirmation of IDH2-mutated disease from a bone marrow sample for subjects in Phase 2 will be based on central laboratory testing performed prior to treatment. A separate tumor (blood and/or bone marrow) sample will be required for central laboratory biomarker analysis (see Section 10.5). A buccal swab for germ-line mutation analysis will be obtained at screening.
[12] Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, and blast count.
[13] If performed, the results and/or samples of hematological assessments, bone marrow biopsies, aspirates, peripheral blood for molecular and functional studies of blasts and neutrophils, and evaluation of the extent of disease and response to treatment will be collected and assessed as part of the study for subjects who undergo HSCT after discontinuation of AG-221. These subjects will be followed at least monthly for assessment of disease response until relapse or end of study.
[14] Sodium, potassium, chloride, calcium, magnesium, phosphorus, carbon dioxide (CO_2), bicarbonate (HCO_3), albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, and indirect bilirubin. In addition, creatine kinase, cardiac troponin, amylase, and lipase are to be obtained at screening, on Day 1 of each treatment cycle, and at the End of Treatment visit.
[15] Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
[16] A serum pregnancy test will be performed at screening (within 7 days prior to first study drug administration) and at the EOT. A urine pregnancy test must be conducted on the day of first study drug administration and confirmed negative prior dosing (Day -3 for subjects undergoing 72-hour PK/PD profile or on C1D1) and Day 1 of all subsequent cycles.
[17] Bone marrow aspirates and core sampling should be performed and analyzed at the local site's laboratory in accordance with the International Council for Standardization in Hematology (ICSH) Guidelines (Lee, et al. 2008) (see Section 10.7). Investigator assessment of cytogenetic risk group at baseline and results of the bone marrow assessments performed for the evaluation of clinical activity will be collected for an independent review during Phase 2 of the study. Analyses should include cytogenetics and flow cytometry according to institutional standards and results should be recorded in the eCRFs. Studies should be conducted on peripheral blood samples if bone marrow aspirate is not available (e.g., a "dry" tap).
[18] Evaluation of disease response, including bone marrow and peripheral blood for plasma and IDH2-mutated cells to be conducted on C2D1, every 28 days during treatment through at least Month 12 (see Section 10.8.1). Evaluation should be independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. After at least 12 months, subjects in the Phase 2 portion of the trial, may have the extent of their disease assessed, including bone marrow biopsy, aspirates or peripheral blood based on their response to treatment.
[19] Subjects will have the extent of their disease assessed based on modified IWG criteria or other appropriate response criteria for the malignancy under study (see Section 10.8).
[20] Response to treatment is to be assessed at this visit if the subject discontinues treatment for reasons other than disease progression.
[21] Subjects are also to be evaluated for RBC and platelet transfusions (dates and units administered) and associated hemoglobin levels and/or platelet counts at each response assessment and as clinically indicated.

[22] The daily dose on C1D1, C1D2, C2D1, C2D2 and C3D1 are to occur in clinic to accommodate PK/PD sampling (C1D1 and C2D1) or to allow for predose assessments (C1D2, C2D2 and C3D1).
[23] Treatment compliance is to be assessed based on return of unused drug as well as subject diaries.
[24] Refer to Table 5 for complete serial PK/PD sampling schedule and to Section 10.10 for details for blood sampling for 2-HG and α-KG.
[25] Any serious adverse events (SAEs) that are assessed by the Investigator as possibly or probably related to study treatment that occur >28 days post-treatment also are to be reported.
[26] Subjects who do not go to HSCT are considered to have completed the study at the time of the Day +28 follow-up assessment; subjects who undergo HSCT after discontinuation of AG-221 remain on study until relapse (or end of study). All subjects enter the survival follow-up phase after study completion.
[27] After the safety follow-up assessments, or for subjects who relapse after HSCT and elect not to restart treatment, subjects are to be contacted every 28 days to assess survival status until death or end of study. All subjects are to be followed for survival status follow up every 3 months until death or end of study.

[28] All new anti-neoplastic therapies administered after the last dose of AG-221 are to be captured for all subjects through end of study.

[29] Starting at Cycle 13, all assessments may be reduced to every 3 cycles unless otherwise indicated.
[30] Starting at Cycle 13, 3 Cycles of AG-221 should be dispensed.
[31] Adverse events and concomitant medication must still be captured every 28 days. On cycle Day 1 (every (28 days) when assessments are not performed documented phone contact is acceptable.

Table 4: Pharmacokinetic and Pharmacodynamic Sampling and Electrocardiogram Schedule for the Phase 1 Dose Escalation and Part 1 Expansion

Visit/Cycle:	Scrn				Cycle 1									Cycle 2					Cycle 3				Cycle 4 – Cycle 12						F/U
Study Day:	D -28	D -3[1,2]			D1[3]		D8		D15			D22		D1			D15		D1			D15	D1			EOT			D +28
Assessment	Blood/ Urine/ ECG[4]	Blood	Urine	ECG	Blood/ Urine	ECG	Blood	ECG	Blood	Urine	ECG	Blood	ECG	Blood	Urine	ECG	Blood	ECG	Blood	Urine	ECG	Blood	Blood	Urine	ECG	Blood	Urine	ECG	ECG
Predose	X	X	X	X	X	X	X		X	X		X		X	X		X		X	X		X	X	X					
Post-dose																														
Anytime								X			X		X			X		X			X				X		X	X	X	X	X
0.5 hr		X[6]		X[6]		X[6]			X[6]					X[6]									X[6,7]							
1 hr		X[6]							X[6]					X[6]									X[6,7]							
2 hr		X[6]		X[8]		X[8]			X[6]					X[6]									X[6,7]							
3 hr		X[6]							X[6]					X[6]									X[6,7]							
4 hr		X[6]		X[8]		X[8]			X[6]					X[6]									X[6,7]							
6 hr		X[6]		X[8]		X[8]			X[6]					X[6]									X[6,7]							
8 hr		X[6]		X[8]		X[8]			X[6]					X[6]									X[6,7]							
10 hr		X[6]	X						X[6]					X[6]									X[6,7]							
24 hr		X[9]	X																											
48 hr		X[9]	X																											
72 hr		X[9]	X																											

Footnotes continue on next page

D = day; ECG = electrocardiogram, EOT = end of treatment, F/U = follow-up and follow-up post HSCT, Scrn = screening
Notes: For all days with predose samples, subjects should be instructed to take their dose of AG-221 in clinic. All 12-lead ECGs are to be conducted after 3 minutes of recumbency. A 12-lead single ECG should also be obtained as clinically indicated. Serial ECGs (Day -3 or C1D1) should be obtained following vital signs assessments. A subset of samples collected for pharmacokinetic (PK) also will be used to assess cholesterol and 4β-OH-cholesterol levels (Section 10.11).

[1] Day -3 assessments, including 72-hour PK/PD and serial 12-lead ECGs will be conducted for the first 3 subjects enrolled in each cohort during the dose escalation phase and the first 15 subjects in each arm of Part 1 Expansion following a single dose of AG-221 administered on Day -3; these procedures are optional (based on Medical Monitor evaluation) for any additional subjects enrolled in these cohorts. All screening assessments must be completed prior to single dose administration on Day -3.
[2] Five urine collections will be obtained during the 72-hour PK/PD sampling time: predose (at least 20 mL) and at the 10-, 24-, 48- and 72-hour blood draws (±1 hour).
[3] Only for subjects who did not undergo the Day -3 assessments. Additional urine samples are required during the treatment period for PD assessment (2-hydroxyglutarate [2 HG] and α-ketoglutarate [α-KG]).
[4] To be obtained within 30 minutes before dose; can be done at any time during screening.
[5] Screening blood sample for analysis of 2-HG and α-KG only.
[6] To be obtained within ±10 minutes of specified time.
[7] Assessments to be conducted on C4D1 only
[8] To be obtained within ±15 minutes of specified time.
[9] To be obtained within ±1 hour of specified time.

Table 5: Pharmacokinetic and Pharmacodynamic Sampling and Electrocardiogram Schedule for Phase 2

Visit/Cycle:	Screening	Cycle 1			Cycle 2			Cycle 3		EOT		F/U
Study Day:	D -28	D1		D2	D1		D2	D1				D+28
Assessment	Blood[1] / Single ECG[3]	Blood	Triplicate ECG[2]	Blood	Blood	Triplicate ECG[2]	Blood	Blood[4]	Single ECG	Blood	Triplicate ECG[2]	Single ECG
Predose	X	X	X	X	X	X	X	X		X		
Post-dose												
2 hr		X[5]	X[6]		X[5]	X[6]						
4 hr		X[5]	X[6]		X[5]	X[6]						
6 hr		X[5]	X[6]		X[5]	X[6]						
8 hr		X[5]			X[5]							
Anytime									X		X	X

D = day; ECG = electrocardiogram, EOT = end of treatment, F/U = follow-up and follow-up post HSCT

Notes: PK refers to blood sample only. For all days with predose samples, subjects should be instructed to take their dose of AG-221 in clinic. All 12-lead ECGs are to be conducted after 3 minutes of recumbency. A 12-lead single ECG should also be obtained as clinically indicated.

[1] Screening blood sample for analysis of 2-hydroxyglutarate (2-HG) and α-ketoglutarate (α-KG) only.

[2] 12-lead triplicate ECGs, done approximately 2 minutes apart, are to be obtained at Day 1 of Cycles 1 and 2 and at EOT. ECGs should be done before pharmacokinetic (PK) sampling on these days.

[3] To be obtained within 30 minutes before dose. Can be done at any time during screening.

[4] Required on C3D1 only; not subsequent cycles.

[5] To be obtained within ±10 minutes of specified time. When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample (within 10 minutes).

[6] ECG to be obtained within ±15 minutes of specified time.

10.2. Informed Consent

A complete description of the study is to be presented to each potential subject and a signed and dated informed consent is to be obtained before any study specific procedures are performed.

10.3. Information to be Collected on Screen Failures

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

10.4. Demographic Data and Medical, Surgical, and Medication History

Subject demographic data, including gender, date of birth, age, race, and ethnicity, will be obtained during screening. A complete medical and surgical history, including the type of underlying malignancy and the date of confirmation of the histologic diagnosis of the underlying malignancy (including reports of bone marrow aspirate and/or biopsy, peripheral blood smear, cytogenetics and other tests if pertinent), will be obtained during screening.

The medical history is to include all relevant prior medical history as well as all current medical conditions.

Prior therapies include surgery, radiation, systemic or any other therapy for the subject's underlying malignancy, particularly induction/re-induction/salvage chemotherapies, consolidation or maintenance therapies, HSCT, low-intensity AML therapies such as azacitidine, decitabine or low dose cytarabine (LDAC), or other medications considered supportive care for AML, regardless of discontinuation date of treatment.

Information supporting CR/CRi/CRp attained during prior AML therapies by local pathology and cytogenetics review, including reports of bone marrow aspirate and/or biopsy, peripheral blood smear, cytogenetics, hematology and other tests if pertinent.

For subjects in the Phase 2 portion of the trial, red blood cell and platelet transfusion history, including dates of the transfusion and units administered, as well as the associated hemoglobin levels and/or platelet counts, must be captured for the 8-week period prior to C1D1.

10.5. Gene Mutation Analysis

For subjects in the dose escalation phase and Expansion Part 1, analysis of cells for IDH2 gene mutated disease, is to be evaluated at screening (if not evaluated previously) by the site's local laboratory to determine subject eligibility for the study (report collected as a source document). For subjects enrolled in the Phase 2 portion of the trial , analysis of cells for IDH2-gene mutated disease will be evaluated at screening by a central laboratory to determine subject eligibility for the study.

Screening bone marrow aspirate **and** peripheral blood samples are required all subjects. In addition:

- A buccal swab for germ-line mutation analysis also will be obtained at screening in all subjects.
- A pre-treatment tumor sample (from blood and bone marrow) will be required for all screened subjects for central laboratory biomarker analysis.
- A blood sample is to be obtained at screening for determination of UGT1A1 mutation status.

10.6. Safety Assessments

10.6.1. Physical Examination and ECOG Performance Status

A complete physical examination, including assessment of weight, will be obtained at screening and at the End of Treatment visit. A limited physical examination will be completed on Day -3 (for subjects undergoing 72-hour PK/PD profile), on Days 1, 8 and 15 of Cycle 1, and on Day 1 of each treatment cycle through at least Cycle 12, and every 3 cycles thereafter. Height will be obtained at the screening visit.

Determination of ECOG PS will be performed at screening, on Day -3 (for subjects undergoing 72-hour PK/PD profile), on Days 1 and 15 of Cycle 1, on Day 1 of each treatment cycle through at least Cycle 12, and every 3 cycles thereafter, at the End of Treatment visit, and at the Follow-up visit. See Appendix 15.5 for ECOG PS scoring.

10.6.2. Vital Signs

Vital signs, including systolic and diastolic BP, heart rate, respiratory rate, and temperature, will be obtained at screening, on Day 15 of Cycle 1, on Day 1 of every treatment cycle through at least Cycle 12, and every 3 cycles thereafter, and at the End of Treatment visit. Assessments should be conducted while the subject is seated or supine.

Additionally, serial vital signs are to be obtained following the first dose of study treatment (i.e., on Day -3 for subjects undergoing the 72-hour PK/PD profile or on C1D1 for subjects who do not attend the Day -3 assessment) at the following times: predose, and 30 ± 10 minutes and 2, 4, 6, and 8 hours (± 15 minutes) post dose following the morning administration of study drug. Note that subjects should be instructed to take their dose of AG-221 in clinic on these days.

10.6.3. Electrocardiogram and Assessment of Left Ventricular Ejection Fraction

See Table 4 and Table 5 for the schedule of ECG assessments.

For subjects in the dose escalation phase and Part 1 Expansion, a single 12-lead ECG is to be obtained at screening, on Days 8, 15, and 22 of Cycle 1, on Days 1 and 15 of Cycle 2, on Day 1 of each treatment cycle thereafter through at least Cycle 12, at the End of Treatment visit, and at the Follow-up visit. A single 12-lead ECG should also be obtained as clinically indicated.

Additionally, serial single 12-lead ECGs are to be obtained in subjects in the dose escalation phase and Part 1 Expansion following the first dose of study treatment (i.e., on Day -3 for subjects undergoing the 72-hour PK/PD profile or on C1D1 for subjects who do not attend the Day -3 assessment) at the following times: predose, and 30 ± 10 minutes and 2, 4, 6, and 8 hours (± 15 minutes) post dose following the morning administration of study drug. Serial single ECGs

should be obtained following vital signs assessments. Note that subjects should be instructed to take their dose of AG-221 in clinic on these days.

For subjects in The Phase 2 portion of the trial, triplicate 12-lead ECGs, obtained approximately 2 minutes apart, are to be obtained predose and 2, 4, and 6 hours (± 15 minutes) post-dose on Day 1 of Cycles 1 and 2; a triplicate ECG is also to be obtained at the End of Treatment visit. When the timing of a blood sample for PK/PD coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample (within 10 minutes). Note that subjects should be instructed to take their dose of AG-221 in clinic on these days. Single 12-lead ECGs are to be obtained in these subjects at screening, anytime post-dose on Day 1 of all cycles beginning with Cycle 3 through at least Cycle 12, and at the Follow-up visit. A single 12-lead ECG should also be obtained as clinically indicated.

All single and triplicate 12-lead ECGs should be obtained following 3 minutes of recumbency.

All subjects are to have LVEF determined by ECHO or MUGA within 28 days of C1D1; repeat assessments are to be conducted on C3D1, Day 1 of every other treatment cycle thereafter (e.g., C5D1, D7D1, etc) through at least Cycle 12, at the End of Treatment visit, and at the Follow-up visit. The same procedure to evaluate LVEF should be conducted throughout the study.

10.6.4. Safety Laboratory Assessments

Clinical laboratory evaluations are to be performed by the site's local laboratory. Prior to starting the study, the Investigator will provide to the Sponsor (or its designee) copies of all laboratory certifications and normal ranges for all laboratory parameters to be performed by that laboratory.

Clinical laboratory evaluations are to be conducted according to the schedule of assessments (Table 2 and Table 3). In addition, all clinically significant laboratory abnormalities noted on testing will be followed by repeat testing and further investigated according to the judgment of the Investigator.

The following safety laboratory parameters are to be evaluated by the Investigator:

Hematology: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, blast count

Chemistry: sodium, potassium, chloride, calcium, magnesium, phosphorus, CO_2, bicarbonate (HCO_3), albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase (LDH), ALP, AST, ALT, total bilirubin, direct bilirubin, indirect bilirubin

Serum Studies: creatine kinase, cardiac troponin, amylase, and lipase

Coagulation Studies: prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)

Fasting Lipid Panel: total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides

Blood for hematology and serum chemistries is to be obtained at screening, Day -3 (for subjects undergoing 72-hour PK/PD profile), Days 1, 8, 15, and 22 of Cycle 1, on Days 1 and 15 of each treatment cycle through at least Cycle 12, and every 3 cycles thereafter, and at the End of Treatment (EOT) visit. For subjects who undergo HSCT following discontinuation of AG-221,

all hematological assessments (e.g., complete blood count) that are performed are to be reported on the eCRF until relapse or end of study.

Blood for creatine kinase, cardiac troponin, amylase, and lipase is to be obtained at screening, Day -3 (for subjects undergoing 72-hour PK/PD profile), on Day 1 of each treatment cycle through at least Cycle 12, and every 3 cycles thereafter, and at the End of Treatment visit.

Blood for coagulation studies is to be obtained at screening, Day -3 (for subjects undergoing 72-hour PK/PD profile), Days 1 and 15 of Cycle 1, Day 1 of each treatment cycle through at least Cycle 12, and every 3 cycles thereafter, and at the End of Treatment visit.

Blood for the fasting lipid panel is to be obtained at screening, every 6 cycles thereafter on treatment through at least Cycle 12, and every 3 cycles thereafter, and at the End of Treatment visit.

Pregnancy Test: All women of child-bearing potential must have a negative pregnancy test to be eligible. A serum pregnancy test will be performed at screening (within 7 days prior to first study drug administration); a urine pregnancy test must be conducted and confirmed negative on the first day of study drug administration before dosing (Day -3 for subjects undergoing 72-hour PK/PD profile or on C1D1) and on Day 1 of each cycle through at least Cycle 12, and every 3 cycles thereafter, and at the EOT visit.

10.6.5. Adverse Events

[redacted]

10.7. Bone Marrow Samples and Peripheral Blood Leukemic Blast Cells

Screening bone marrow aspirate **and** peripheral blood samples are required all subjects. A bone marrow biopsy must be collected if adequate aspirate is not attainable unless:

- A bone marrow aspirate and biopsy was performed as part of the standard of care within 28 days prior to the start of the study treatment; and
- Slides of bone marrow aspirate, biopsy and stained peripheral blood smear are available for both local and central pathology reviewers; and

- A bone marrow aspirate sample acquired within 28 days prior to the start of study treatment has been sent for cytogenetic analysis.

For subjects in the dose escalation phase and Part 1 Expansion, bone marrow biopsies and/or aspirates are to be obtained at screening, C1D15, C2D1, C3D1, every 56 days through at least Month 12 independent of dose delays and/or interruptions, at any time when progression of disease is suspected, and at the End of Treatment visit.

Starting at Cycle 13, at a minimum, subjects in remission will require a BMA/BMB when blood counts suggest possible relapse or progression of disease unless the local standard of care (SOC) required more frequent bone marrow samples. For those subjects, not in remission, it is reasonable to perform a bone marrow aspiration/biopsy every 1 to 2 months to assess for response.

Note that the Cycle 1 Day 15 bone marrow evaluation should not be used to determine study treatment continuation status in any subject.

For subjects in the Phase 2 portion of the trial, bone marrow aspirates and peripheral blood are to be obtained at screening, C2D1, every 28 days thereafter through at least Cycle 12 independent of dose delays and/or interruptions, at any time when progression of disease is suspected, and at the End of Treatment (EOT) visit. For those subjects who undergo HSCT following discontinuation of AG-221, results of any bone marrow biopsies and/or aspirates that are performed are to be reported on the eCRF until relapse or end of study.

Starting at Cycle 13, at minimum, a subject in remission will require a BMA/BMB when blood counts suggest possible relapse or progression of disease unless the local standard of care (SOC) required more frequent bone marrow samples. For those patients, not in remission, it is reasonable to perform a bone marrow aspiration/biopsy every 1 to 2 months to assess for response.

Results of the bone marrow assessments performed for the evaluation of clinical activity will be collected for evaluation retrospectively by an IRAC for subjects in the Phase 2 portion of the trial of the study.

Bone marrow aspirates and core sampling should be performed according to standard of care and analyzed at the local site's laboratory in accordance with the International Council for Standardization in Hematology (ICSH) Guidelines (Lee, et al. 2008).

The diagnosis and evaluation of AML or MDS can be made by bone marrow aspiration when a core sample is unobtainable and/or is not a part of the standard of care. A bone marrow biopsy is required in case of dry tap or failure (mainly dilution) with the aspiration.

Bone marrow core biopsies and aspirates are to be evaluated for morphology, flow cytometry, and for karyotype to assess potential clinical activity (see Section 10.8).

Samples of the bone marrow and peripheral blood blast cells and neutrophils also will be evaluated at central laboratories for 2-HG and α-KG levels, gene expression profiles, histone and DNA methylation patterns, and metabolomic profiling.

Peripheral blood for the evaluation of plasma and IDH2-mutated cells, including leukemic blasts and neutrophils, (see Section 10.5) is to be obtained at screening, C1D15 (dose escalation and Part 1 Expansion only) C2D1, every 28 days through Month 12, and every 3 cycles thereafter

independent of dose delays and/or interruptions, at any time when progression of disease is suspected, and at the EOT visit. For those subjects who undergo HSCT following discontinuation of AG-221, any peripheral blood evaluations that are conducted should be assessed for plasma and IDH2-mutated cells, including leukemic blasts and neutrophils until relapse or end of study.

Cell counts and flow cytometry will be used to assess the state of differentiation of blast cells collected from bone marrow and peripheral blood. Side scatter also will be analyzed to determine the complexity of the blast cells in response to AG-221.

Instructions for the processing, storage, and shipment of samples for central analysis will be provided in a separate study manual.

10.8. Clinical Activity Assessments

The clinical activity of AG-221 will be evaluated by assessing response to treatment according to the 2003 revised IWG criteria for AML (Cheson, et al. 2003) or the 2006 modified IWG criteria for MDS (Cheson, et al. 2006) (see also Section 10.7).

10.8.1. Phase 1 (Dose Escalation and Part 1 Expansion)

For subjects in Arm 4 of Part 1 Expansion with other IDH2-positive hematologic malignancies, e.g., multiple myeloma (MM), essential thrombocythemia (ET) or polycythemia vera (PCV), or myelofibrosis (MF), other appropriate response criteria for the malignancy should be used [i.e., the International Myeloma Working Group criteria for subjects with MM (Durie, et al. 2006) or the revised response criteria for ET/PCV (Barosi, et al. 2013) or MF (Tefferi, et al. 2013)].

Disease response to treatment will be assessed through the evaluation of bone marrow biopsies and/or aspirates, along with complete blood counts and examination of peripheral blood films.

Eligibility and treatment decisions in all subjects will be determined by the Investigators based on IWG response criteria or other appropriate response criteria for the malignancy under study (Section 10.8).

Subjects in the dose escalation phase and Part 1 Expansion will have the extent of their disease assessed and recorded at screening, on C1D15, C2D1, C3D1, and every 56 days while on study drug treatment through at least Month 12, independent of dose-delays and/or dose interruptions, and/or at any time when progression of disease is suspected. An assessment also will be conducted at the End of Treatment visit for subjects who discontinue the study due to reasons other than disease progression.

Starting at Cycle 13, subjects in the dose escalation phase and Part 1 Expansion in remission may have the extent of their disease assessed every 3 cycles (via bone marrow biopsy, aspirates or peripheral blood) unless the local standard of care (SOC) requires more frequent extent of disease assessments. For those subjects not in remission, it is reasonable to have the extent of their disease assessed every 1 to 2 months to assess for response.

10.8.2. Phase 2

In the Phase 2 portion of the trial, eligibility, treatment decisions, and response to treatment will be determined by the Investigators based on modified International Working Group (IWG) response criteria (Table 7 and Table 8). Response will be also be assessed retrospectively by an Independent Response Adjudication Committee (IRAC). Subjects in the Phase 2 portion of the trial will have the extent of their disease assessed and recorded at screening, on C2D1, every 28 days thereafter through at least Cycle 12 while on study drug treatment, independent of dose-delays and/or dose interruptions, and/or at any time when progression of disease is suspected. An assessment also will be conducted at the End of Treatment visit for subjects who discontinue the study due to reasons other than disease progression. For those subjects who undergo HSCT following discontinuation of AG-221, disease response assessments are to be conducted at least monthly until relapse or end of study.

Starting at Cycle 13, subjects in Phase 2 in remission may have the extent of their disease assessed every 3 cycles (via bone marrow biopsy, aspirates or peripheral blood) unless the local standard of care (SOC) requires more frequent extent of disease assessments. For those subjects

not in remission, it is reasonable to have the extent of their disease assessed every 1 to 2 months to assess for response.

Subjects in the Phase 2 portion of the trial will also be evaluated for RBC and platelet transfusion requirements, including dates of the transfusion and units administered, as well as the associated hemoglobin levels and/or platelet counts, at each disease response assessment.

10.8.3. Assessment of Response Criteria

Evidence supports that cancer-associated IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal production of 2-HG, a potential oncometabolite (Figure 3). AG-221 may produce antitumor effects by reversing the differentiation block induced by the IDH2 mutations and promoting appropriate cellular differentiation.

The response pattern seen with such mechanism of action may extend beyond the typical time course of responses seen with cytotoxic agents, and can generate a clinical response after an initial increase in the number of immature monocytes or blast cells, and increase in cellularity in the bone marrow, onset of cytopenia after initial rise in platelets, or appearance of differentiation-like syndrome.

Standard assessment criteria developed based on the experience from the cytotoxic chemotherapeutic agents may not provide a complete and accurate response assessment for this novel class of IDH2 inhibitors. Therefore, in the setting where a subject's assessment shows signs similar to progression within the first 2 cycles, caution should be exercised in discontinuing study drug, and a discussion with the Medical Monitor is required, especially in situations where the subject's clinical condition is stable as supported by, but limited to, absence of signs and symptoms of rapid deterioration indicating disease progression and/or general condition is stable or improving.

Note that for subjects enrolled in the Phase 1 portion of the trial, the C1D15 bone marrow evaluation should not be used to determine study treatment continuation status in any subject.

Subjects who experience progression of disease (PD) per the applicable response criteria should have assessment of the disease repeated 28 days later in order to confirm PD with option of continuing treatment as described above while awaiting for confirmation. If repeat evaluation confirms PD, subjects will discontinue study treatment and proceed to the survival follow-up phase (see Table 6 for general guidance).

Table 6: Disease Assessment and Treatment after 1st Evidence of Disease Progression

	Clinically Stable		Clinically Unstable	
	Disease Assessment[1, 2]	**Treatment**	**Disease Assessment[1, 2]**	**Treatment**
1st evidence of PD or signs of differentiation like syndrome	Repeat assessment 28 days after first sign of progression for confirmation	Continue study treatment at the Investigator's discretion while awaiting for confirmatory assessment	Repeat assessment 28 days after first sign of progression for confirmation if possible	May discontinue study treatment at Investigator's discretion while awaiting for confirmatory assessment
If repeat evaluation shows SD, PR, or CR	Continue regularly scheduled assessment as per schedule of event	Continue study treatment	Continue regularly scheduled assessment as per schedule of event	Continue study treatment
If repeat evaluation confirms PD	No additional assessment required	Discontinue study treatment	No additional assessment required	Discontinue study treatment

[1]Subjects in the dose escalation phase and Part 1 Expansion will have the extent of their disease assessed and recorded at screening, on Days C1D15, C2D1, and C3D1, every 56 days thereafter while on study drug treatment, independent of dose-delays and/or dose interruptions, and/or at any time when progression of disease is suspected.

[2]Subjects in the Phase 2 portion of the trial will have the extent of their disease assessed and recorded at screening, on C2D1, every 28 days thereafter through 12 months and then every 56 days while on study drug treatment, independent of dose-delays and/or dose interruptions, and/or at any time when progression of disease is suspected.

Note that subjects with stable or progressive disease may continue to receive study treatment with AG-221 at the discretion of the Investigator and with Medical Monitor approval.

The following criteria outlined in Table 7, Table 8, Table 9 and Table 10 will be used to assess response to treatment for subjects with AML (Table 7 and/or Table 8) and MDS (Table 9 and Table 10). For subjects with other IDH2-positive hematologic malignancies other appropriate response criteria for the malignancy should be used.

Table 7: Proposed Modified International Working Group Response Criteria for Acute Myeloid Leukemia

Category	Definition
Complete remission (CR)*	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L (1000/µL); platelet count >100 x 10^9/L (100,000/µL); independence of red cell transfusions
CR with incomplete platelet recovery (CRp)	All CR criteria except for residual thrombocytopenia (platelet counts <100 x 10^9/L [100,000/µL])
CR with incomplete recovery (CRi)•	All CR criteria except for residual neutropenia (absolute neutrophil count <1.0 x 10^9/L [1000/µL])
Cytogenetic CR (CRc)◊	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)§	No standard definition; depends on molecular target
Morphologic leukemia-free stateΔ	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase I and II clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; Phase 2/3 trials), or failure to achieve CR, CRi or PR (Phase 1 trials); only includes patients surviving ≥7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse (defined only for subjects who have previously attained CR, Cri, CRp or MLFS)¥	Bone marrow blasts ≥5 percent; or reappearance of blasts in the blood; or development of extramedullary disease

Source: (Cheson, et al. 2003)

Footnotes on next page

* All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

• The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

Δ This category may be useful in the clinical development of novel agents within phase I clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

(Footnotes continued on next page)

◊ Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome.

§ As an example, in core-binding factor AML low-level polymerase chain reaction-positivity can be detected in patients even in long-term remission. Normalizing to 104 copies of ABL1 in accordance with standardized criteria, transcript levels below 10 to 12 copies appear to be predictive for long-term remission.

¥ -. A repeat marrow should be performed to confirm relapse with 2 consecutive assessments separated by at least 1 month. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Table 8: Criteria for Stable Disease and Progressive Disease for Acute Myelogenous Leukemia

Category	Response criteria
Stable disease	Failure to achieve a response and not meeting the criteria for disease progression
Disease progression (defined only for subjects who have previously attained PR or SD)	Progression should be confirmed by 2 consecutive assessments separated by at least 1 month. Development of new biopsy-confirmed extramedullary disease since last disease evaluation The date of progressive disease is defined as the first date of progression. Progression is defined as the following: For patients with 5 to 67% bone marrow blasts at nadir: - a >50% increase in bone marrow blast count percentage from the nadir and that is ≥20%. For patients with ≥67% bone marrow blasts at nadir: - a doubling of the nadir absolute peripheral blood blast count and the final absolute peripheral blood blast count is >10 x 10^9/L.

Table 9: Proposed Modified International Working Group Response Criteria for Altering Natural History of MDS

Category	Response criteria (Responses must last at least 4 weeks)
Complete remission	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥11 g/dL
	Platelets ≥100 × 10^9/L
	Neutrophils ≥1.0 × 10^9/L†
	Blasts = 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥50% over pretreatment but still >5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones
	Partial: At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥50% increase in blasts to >5% blasts
	5%-10% blasts: ≥50% increase to >10% blasts
	10%-20% blasts: ≥50% increase to >20% blasts
	20%-30% blasts: ≥50% increase to >30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥2 g/dL
	Transfusion dependence

Source: (Cheson, et al. 2006)

AML = acute myeloid leukemia; CR = complete remission; DFS = disease-free survival; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; MDS = myelodysplastic syndromes; PFS = progression-free survival; PR = partial remission.

Note: Deletions to International Working Group (IWG) response criteria are not shown.

Note: To convert hemoglobin from g/L to g/dL, divide g/L by 10.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).

†Modification to IWG response criteria (Cheson, et al. 2003)

‡In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such subjects can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Table 10: Proposed Modified International Working Group Response Criteria for Hematologic Improvement

Hematologic improvement*	Response criteria (Responses must last at least 8 weeks)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100×10^9/L)	Absolute increase of ≥30×10^9/L for patients starting with >20×10^9/L platelets Increase from <20×10^9/L to >20×10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0×10^9/L)	At least 100% increase and an absolute increase >0.5×10^9/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by > 1.5 g/dL Transfusion dependence

Source: (Cheson, et al. 2006)
Hgb = hemoglobin; HI = hematologic improvement; RBC = red blood cell.
Note: Deletions to the International Working Group (IWG) response criteria are not shown.
Note: To convert hemoglobin from g/L to g/dL, divide g/L by 10.
* Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart (modification).
†Modification to IWG response criteria (Cheson, et al. 2003)
‡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.

10.9. Pharmacokinetic Assessments

10.9.1. Blood Sample Collection and Pharmacokinetic Measurements During Dose Escalation

Serial blood samples will be drawn before and after dosing with AG-221 in order to determine circulating plasma concentrations of AG-221 (and, if technically feasible, the metabolite of AG-221, AGI-16903). The blood samples will also be used for the determination of 2-HG and α-KG, for evaluation of cholesterol, and 4β-OH-cholesterol levels (see Section 10.10.1 and Section 10.11).

For the first 3 subjects enrolled in a cohort during the dose escalation phase and the first 15 subjects enrolled in each arm of Part 1 Expansion (unless approved by the Medical Monitor to omit the assessment), a single dose of AG-221 will be administered on Day -3 (i.e., 3 days prior to their scheduled C1D1 dose). Blood samples will be drawn prior to the single-dose administration of AG-221 (within 30 minutes) and at the following time points after administration: 30 (±10) minutes and 1, 2, 3, 4, 6, 8, and 10 hours, (±10 minutes), and 24, 48, and 72 hours (±1 hour). After 72 hours of blood sample collection, subjects will begin oral daily dosing of AG-221 (i.e., C1D1). The PK/PD profile from Day -3 through Day 1 is optional for additional subjects enrolled in the dose escalation phase (i.e., for any subjects beyond the 3 initial

subjects enrolled in a cohort) and may be required for subjects beyond the initial 15 enrolled in each of the expansion arms based on Medical Monitor decision.

All subjects in the dose escalation phase and Part 1 Expansion will undergo 10-hour PK/PD sampling on C1D15, C2D1, and C4D1. For this profile, one blood sample will be drawn immediately prior to (within 30 minutes) that day's first dose of AG-221 (i.e., dosing with AG-221 will occur at the clinical site); subsequent blood samples will be drawn at the following time points after dosing: 30 minutes, and 1, 2, 3, 4, 6, 8, and 10 hours (±10 minutes).

Predose blood samples (trough) will be obtained for subjects in the dose escalation phase and Part 1 Expansion on C1D1 (for those subjects who did not undergo the Day -3 sampling), C1D8, C1D22, C2D15, C3D1, C3D15, C5D1 and Day 1 of all cycles through cycle 12 for determination of AG-221 concentrations, as well as 2-HG and α-KG concentrations (see Section 10.10.1). Additionally, blood samples will be drawn at the End of Treatment Visit (EOT).

For subjects in the Phase 2 portion of the trial, blood samples for PK assessment will be drawn on C1D1 predose (within 30 minutes) and post-dose at the following time points: 2, 4, 6, and 8 hours (±10 minutes); and on C2D1 predose (within 30 minutes) and post-dose at the following time points: 2, 4, 6, and 8 hours (±10 minutes). Additional blood samples for PK/PD assessments will be drawn on C1D2, C2D2, and C3D1 predose (within 30 minutes). In addition, blood samples for PK/PD assessments will also be drawn at the EOT visit.

When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample (within 10 minutes). The timing of blood samples drawn for AG-221 concentration determination may be changed if the emerging data indicates that an alteration in the sampling scheme is needed to better characterize AG-221's PK profile.

See also Table 4 and Table 5 for the schedule of PK/PD assessments.

10.9.2. Urine Collection

For the first 3 subjects enrolled in a cohort during the dose escalation phase and the first 15 subjects enrolled in each arm of Part 1 Expansion (unless approved by the Medical Monitor to omit the assessment), urine will be collected on Day -3 prior to and over the first 72 hours following a single dose of AG-221 to provide a preliminary estimate of the extent to which AG-221 (and, if technically feasible, the potential metabolite of AG-221, AGI-16903) is eliminated unchanged in the urine. Samples also will be analyzed for 2-HG and α-KG concentrations and for urinary creatinine concentration (see Section 10.10.2). Urine samples are not required for subjects enrolled in the Phase 2 portion of the trial.

Five urine collections will be obtained during this 72-hour period. An initial urine collection will be obtained prior to AG-221 dosing (at least 20 mL). Subsequent collections will be obtained at the time of the 10-, 24-, 48- and 72-hour blood draws (±1 hour). Additionally, a urine collection (at least 20 mL) will occur at the End of Treatment Visit.

The serial urine sampling from Day -3 through Day 1 is optional for additional subjects enrolled in the dose escalation phase (i.e., for any subjects beyond the 3 initial subjects enrolled in a cohort) and for subjects beyond the initial 15 enrolled in each of the Part 1 Expansion arms. For

subjects in the dose escalation phase and Part 1 Expansion who do not have the Day -3 through Day 1 serial urine sampling, a predose urine sample is required on C1D1.

Urine samples are not required for subjects enrolled in the Phase 2 portion of the trial.

The volume of each collection will be measured and recorded and sent to a central laboratory for determination of the urinary AG-221 concentration.

10.10. Pharmacodynamic Assessments

10.10.1. Blood Samples

Serial blood samples will be drawn before and after dosing with AG-221 in order to determine circulating concentrations of 2-HG and α-KG. Samples collected for PK assessments also will be used to assess 2-HG and α-KG levels (see Section 10.9.1). In addition, subjects will have blood drawn for determination of 2-HG and α-KG levels at the screening assessment.

The timing of blood samples drawn for 2-HG and α-KG concentration determination may be changed if the emerging data indicate that an alteration in the sampling scheme is needed to better characterize the 2-HG and/or α-KG response to AG-221 treatment.

Bone marrow also will be assessed for 2-HG and α-KG levels, see Section 10.7.

10.10.2. Urine Samples

Urine will be collected from subjects in the dose escalation phase and Part 1 Expansion phase before and after dosing with AG-221 for the determination of concentrations of 2-HG and α-KG. Samples collected for PK assessments on Day -3 through Day 1 will also be used to assess 2-HG and α-KG levels (see Section 10.9.2). In addition, subjects will have urine sample collected for determination of 2-HG and α-KG levels at the screening assessment and the End of Treatment visit.

In addition, for all subjects, a urine collection will occur prior to dosing on Day 15 of Cycle 1 and on Day 1 of Cycle 2 through at least Cycle 12, and every 3 cycles thereafter. At least 20 mL of urine will be collected for each sample.

Urine samples are not required for subjects enrolled in the Phase 2 portion of the trial.

The volume of each collection will be measured and recorded and sent to a central laboratory for determination of urinary 2-HG and α-KG concentration. An aliquot from each collection will be analyzed for urinary creatinine concentration.

10.11. Evaluation of Cholesterol and 4β-OH-Cholesterol

For subjects in the dose escalation phase and Part 1 Expansion, serial blood samples will be drawn to obtain plasma cholesterol and 4β-OH-cholesterol levels as a potential CYP3A4 induction marker. A subset of samples collected for PK assessments also will be used to assess cholesterol and 4β-OH-cholesterol levels (see Section 10.9.1). Specifically, samples obtained at screening and on Day -3 predose (within 30 minutes), and 24, 48, and 72 hours (±1 hour) will be assessed for cholesterol and 4β-OH-cholesterol levels. Samples collected predose on Days 1, 8, 15 and 22 of Cycle 1, Days 1 and 15 of Cycles 2 and 3, and Day 1 of every cycle through at least

Cycle 12, and samples obtained at the End of Treatment visit also will be assessed for cholesterol and 4β-OH-cholesterol levels.

Samples for plasma cholesterol and 4β-OH-cholesterol levels are not required for subjects enrolled in the Phase 2 portion of the trial.

10.12. Sample Processing, Storage, and Shipment

Instructions for the processing, storage and shipment of all study samples for central analysis will be provided in a separate study manual.

12. STATISTICAL METHODS

12.1. Sample Size Estimation

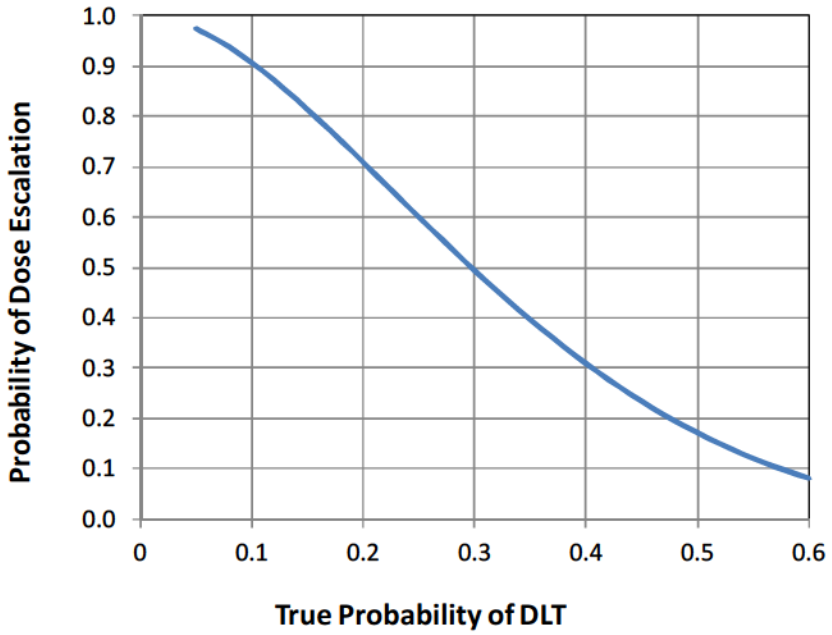
Based on the planned dose escalation scheme (see Section 9.7), it is estimated that approximately a minimum of 291 subjects may be enrolled in the study.

Assuming that identification of the MTD/MAD requires the evaluation of 13 dose levels/schedules of AG-221 with up to 5 subjects per dose level, with the exception that the MTD requires 6 subjects, then 66 subjects will be enrolled during the dose escalation part of the study. Additional subjects may be needed for cohort expansion during dose escalation, for the replacement of subjects who are not evaluable for PK/PD, safety, or clinical activity, or for evaluation of alternative dosing regimens other than the planned escalation scheme or the MTD, to optimize the RP2D and regimen(s). As of April 2015, 5 dose levels (ranging from 30 mg to 150 mg) have been evaluated in the BID schedule and 8 dose levels (ranging from 50 mg to 650 mg) have been evaluated in the QD schedule.

Four cohorts of approximately a minimum of 25 additional subjects in specific hematologic malignancy subsets (total a minimum of 100 subjects) will be enrolled in Part 1 Expansion of the study. The Phase 2 will enroll approximately 125 subjects with relapsed or refractory AML with an IDH2 mutation.

Figure 8 present the probability of escalation from a lower dose to the next higher dose, for a range of true rates of DLT, in the standard 3+3 dose-escalation design. For example, if the true DLT rate were 0.20 (20%), then the chance of dose escalation would be approximately 0.70 (70%).

Figure 8: Probability of Dose Escalation for the 3+3 Design



To ensure acceptable toxicity at the MTD or other doses and regimens that may be used in further studies, approximately 25 additional subjects will be accrued into each of 4 arms in Part 1

Expansion. Based on a sample size of 25 subjects within each arm, there is 93% probability of detecting 1 or more AEs with an underlying rate of 10%, and 72% probability of detecting 1 or more AEs with an underlying rate of 5%.

Phase 2:

An overall objective response rate (ORR, see Section 12.5.7) of at least 33.6% in 125 subjects (at least 42 responses in 125 subjects) will result in an exact binomial 95% CI with a lower bound greater than 25%, which is clinically meaningful in this setting and exceeds the ORR expected with available therapies (Roboz, et al. 2014). If 42 responses in 125 subjects are observed (33.6% observed ORR), the 95% CI will be (25.4%, 42.6%). This will be considered as evidence of clinically significant activity of AG-221.

Additional subjects may be needed for the replacement of subjects who are not evaluable for PK/PD, safety, and/or clinical activity, or for evaluation of alternative dosing regimens.

12.2. Populations for Analysis

The following subject populations (i.e., analysis sets) will be evaluated and used for presentation of the data:

- Full Analysis Set (FAS): All subjects who were enrolled and received at least one dose of study treatment. Subjects will be classified according to the assigned dose level and schedule. The FAS is the primary analysis population for efficacy and will be the default analysis set for all analyses, unless otherwise specified.
- Dose Determining Set (DDS): All dose escalation subjects who either had a DLT during Cycle 1, or who completed at least 75% of their planned Cycle 1 doses (21 out of 28 days) and were considered by the Clinical Study Team to have had sufficient safety data available to conclude that a DLT did not occur during Cycle 1.
- Safety Analysis Set (SAS): 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 SAS will be the primary set for the analysis of safety data.
- Evaluable Analysis Sets
  - Evaluable Analysis Set (EAS): All subjects in the FAS for whom the baseline response assessment and at least one post baseline response assessment at Day 28 or later are available and evaluable.
  - Central Evaluable Analysis Set (CEAS): All subjects in the FAS for whom the baseline response assessment and at least one post baseline response assessment at Day 28 or later are available and evaluable by central independent review.

  Results of the potential clinical activity of AG-221 will be primarily based on the FAS. Additional efficacy analyses will be produced for the EAS and CEAS.
- Pharmacokinetic Analysis Set (PAS): All subjects who have at least one blood sample providing evaluable PK data for AG-221.

12.3. Procedures for Handling Missing, Unused, and Spurious Data

No imputation will be performed for missing data elements.

When tabulating AE data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment emergent. A missing onset date will be coded as the day of treatment.

For the purposes of reporting, subjects continuing to receive study drug will have time-to-event data (e.g., duration of response and EFS) censored at the date of last documented disease assessment prior to the data cutoff date. Further details of censoring rules will be documented in the statistical analysis plan.

Subjects who have disease progression and continue to receive treatment after progression will be considered as having documented progressive disease at the time of first progression and will be counted as progressive disease at that time in primary efficacy analyses. All response assessments occurring after documented progression will be listed and analyzed separately.

Subjects who discontinue AG-221 treatment to receive HSCT will remain on study and will be followed until documented disease progression or end of study.

Subjects with a best overall response of 'Unknown' or 'Not Evaluable' will be considered non-responders in estimating response rates in the efficacy analysis.

12.4. Interim Analyses

The data with the cutoffs of 15 Apr 2016 and 14 Oct 2016 were analyzed to descriptively estimate the efficacy and safety profile of AG-221 for the NDA submission and 4-month safety update. These interim analyses were not intended to modify the study conduct. Interim safety reviews will be conducted by the Clinical Study Team following completion of each dosing cohort prior to dose escalation and enrollment in the next cohort and every 8 weeks during the expansion phase. Evaluation of PK and PD variables will also be conducted as needed to evaluate the potential relationship between levels of AG-221 and 2-HG (and/or α-KG) levels. Evaluation of other data, including baseline information and measures of clinical activity, may be undertaken to provide insight into the dosing regimen and plans for future studies.

12.5. Statistical Methodology

12.5.1. General Methods

Tabulations will be produced for disposition, demographic and baseline disease characteristics, safety, PK, PD, and clinical activity parameters and will be presented by dose level, disease and overall. For analyses of safety and unless otherwise specified, subjects treated during the dose escalation phase will be pooled with those receiving the same dose and regimen during the expansion phase. For analyses of clinical activity, summaries will be produced separately for the

dose escalation, by each arm in Part 1 Expansion, and for the Phase 2 portion of the study. Subjects from the dose escalation and Part 1 Expansion, who meet inclusion and exclusion criteria of Phase 2, may be included in efficacy analyses if treated with the same dose and regimen.

Categorical variables will be summarized by frequency distributions (number and percentages of subjects with 95% confidence interval, if applicable) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum).

All data will be provided in by-subject listings.

The study data will be analyzed and reported based on all subjects' data from the dose escalation and expansion phases up to the time when all subjects have completed at least 6 cycles of treatment regardless of dose interruption or discontinued study drug earlier, or when the follow up is deemed adequate for the assessment of duration of response, whichever is the later date. Any additional data for subjects continuing to receive study treatment or in follow up for HSCT or survival past the data cutoff date for the clinical study report (CSR) will be reported in a final descriptive update at the end of study.

12.5.2. Disposition

A tabulation of the disposition of subjects will be presented, including the number enrolled, the number treated, and the reasons for study discontinuation will be reported. Entry criteria and protocol deviations will be listed.

12.5.3. Baseline Evaluations

Demographic and baseline disease characteristics data summarization will be performed in order to descriptively assess the comparability of dose groups. Data to be tabulated will include sex, age, and race and ethnicity, as well as disease-specific information.

12.5.4. Exposure and Safety Analyses

[redacted]

[redacted] is not a mandatory analysis. α-KG levels may be analyzed on an exploratory basis.

12.5.7. Clinical Activity Analyses

Response to treatment will be assessed by the site Investigator's using modified IWG (see Section 10.8). Additionally, for subjects in Phase 2, response will be assessed by independent central review.

Subjects who discontinue AG-221 treatment to receive HSCT will remain on study and will be followed until documented disease progression or end of study.

For the dose-escalation phase, point estimates and 95% confidence intervals for response rates will be summarized for each dose level and overall; for Part 1 Expansion, these will be summarized by expansion arm. The analysis of Part 1 Expansion arms may also include subjects from the dose-escalation phase who received the same dose/regimen as subjects in the expansion arms and who meet the eligibility criteria of individual arms. Response will be summarized by best objective response categories, complete remission rate (CRR), and overall response rate (ORR), including all responses of CR, CRp, mCR (morphologic leukemia-free state [MLFS]), CRi, and PR. Other measures of clinical activity, including duration of complete remission, duration of response, EFS, overall survival, and time to remission/response will be summarized.

Statistical Considerations for Phase 2

Phase 2 is the pivotal part of this study. The primary objective of Phase 2 is to confirm the preliminary clinical activity observed in the dose escalation and Part 1 Expansion in subjects with IDH2 mutated relapsed or refractory AML at the recommended dose/regimen for expansion. The primary analysis of the clinical activity of AG-221 will be based on Investigator's response assessment (CRR, ORR, and duration of remission/response). The FAS will be used. Key supportive analyses will be based on independent central review of response in FAS. Additional analyses of efficacy will be conducted using the EAS/CEAS. Subjects from the

dose escalation and Expansion Part 1 who meet eligibility criteria for the Phase 2 portion of the trial may be included as a supportive analysis of clinical activity if treated with the same dose and regimen.

An observed ORR of at least 33.6% (at least 42 responses in 125 subjects) will result in an exact binomial 95% CI with a lower bound greater than 25%, which is clinically meaningful in this setting and exceeds the ORR expected with available therapies (Roboz, et al. 2014). This will be considered as evidence of clinically significant activity of AG-221.

Endpoints

Overall response rate (ORR): ORR is defined as the rate of CR, CRp, mCR [MLFS], CRi, and PR.

Complete remission rate (CRR): CRR is defined as the rate of CR.

Duration of response (DOR): Among subjects who have a response of CR, CRp, mCR, CRi, or PR, DOR will be calculated as the date of the first occurrence of response to the date of documented disease relapse, progression or death, including subjects that discontinue AG-221 treatment to receive bone marrow transplantation. Kaplan-Meier methods will be used to estimate DOR, and subjects without relapse, progression or death will be censored at the last response assessment date.

Duration of complete remission (DOCR): Among subjects who have a response of CR, DOCR will be calculated as the date of the first remission to the date of documented disease relapse or death, including subjects that discontinue AG-221 treatment to receive bone marrow transplantation. Kaplan-Meier methods will be used to estimate DOCR, and subjects without relapse or death will be censored at the last response assessment date.

Time to response (TTR): Time to response will be assessed from the date of first dose to the date of first occurrence of response, which includes CR, CRp, mCR/MLFS, CRi, and PR. Subjects without a response will be censored at the date of last response assessment.

Time to Best Response (TTBR): Time to best response will be assessed from the date of first dose to the date of first occurrence of best response. Subjects without a response will be censored at the date of last response assessment.

Time to complete remission (TTCR): Time to complete remission will be assessed from the date of first dose to the date of first remission (CR). Subjects without a remission will be censored at the date of last response assessment.

Event-free survival (EFS): Event-free survival will be calculated from the date of first dose to the date of relapse, progression or death, whichever occurs first. Subjects without an EFS event will be censored at the last response assessment date. Kaplan-Meier methods will be used to estimate EFS, including subjects that discontinue AG-221 treatment to receive bone marrow transplantation.

Overall survival (OS): Overall survival is defined as the time from first dose to the date of death. Subjects who are alive at the analysis cutoff date will be censored at the last contact date.

All subjects are to be followed for survival status follow up every 3 months until death, withdrawal of consent, or end of study for survival.

56-Day transfusion independence rate: The rate of subjects who have been transfusion free for at least 56 consecutive days post baseline during treatment exposure period. Sensitivity analyses will be conducted for all duration of response/remission, time to response/remission, and EFS endpoints in which subjects who go on to receive bone marrow transplantation will be censored at the time of transplantation.

All time to event endpoints will be estimated using Kaplan-Meier methods. Point estimates and 95% confidence intervals will be provided where appropriate. Estimates of the median and other quantiles, as well as individual time points (e.g., 3-month, 6-month, and 12-month rates) will be produced. Additional details of the censoring rules will be specified in the Statistical Analysis Plan. Other measures of clinical activity will be evaluated including summaries of transfusion requirements and infection rates. Descriptive statistics will be used.

12.5.8. Exploratory Analyses

[redacted]

12.6. Procedures for Reporting Deviations to Protocol-defined Statistical Analysis Plan

All deviations from the protocol-defined statistical analysis plan will be provided in the final clinical study report.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigators' Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

13.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (Appendix 15.8).

The Investigator must obtain IRB/IEC approval for the investigation and must submit written documentation of the approval to the Sponsor before he or she can enroll any subject into the study. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC. The IRB/IEC is to be notified of any amendment to the protocol in accordance with local requirements. Progress reports and notifications of serious unexpected adverse drug reactions are to be provided to the IRB/IEC according to local regulations and guidelines.

13.3. Subject Information and Informed Consent

The Investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

After the study has been fully explained, written informed consent will be obtained from either the subject or his/her guardian or legal representative prior to study participation.

The subject's signed and dated informed consent must be obtained before conducting any study-related procedures. The Investigator must maintain the original, signed consent form. A copy of the signed form must be given to the subject.

The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

13.4. Subject Confidentiality

In order to maintain subject privacy, all source documents/eCRFs, study drug accountability records, study reports and communications will identify the subject by initials and the assigned

subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the source documents/eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.5. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable, where regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or Medical Monitor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/eCRF.

13.6. Data Management

All data for the subjects recruited for the trial will be entered onto the eCRFs via an Electronic Data Capture (EDC) system provided by the Sponsor or designee. Only authorized staff may enter data onto the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the site staff.

Electronic case report forms will be checked for correctness against source document data by the Sponsor's monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the Investigator or the study site staff to make appropriate corrections, and the corrected eCRF will again be reviewed for completeness and consistency. Any discrepancies will be noted in the eCRF system by means of electronic data queries. Authorized site staff will be asked to respond to all electronic queries according to the eCRF guidelines.

13.7. Source Document/Case Report Form Completion

Source documents/eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source document/eCRF. The source document/eCRF should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs and subject status.

The Investigator, or designated representative, should complete the source document/eCRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must

be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the source document/eCRF to endorse the recorded data.

The Investigator will retain all completed source documents.

13.8. Direct Access to Source Data

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of the source documents/eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, e-mail, and fax).

All unused study drug and other study materials should be destroyed or returned to the Sponsor or designee after the study has been completed, as directed by the Sponsor.

Regulatory authorities, the IEC/IRB, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, eCRFs, and other study documentation for an on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

13.9. Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

13.10. Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

13.11. Publication of Study Findings and Use of Information

All information regarding AG-221 supplied by the Sponsor or designee to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the

development of AG-221 and a companion diagnostic device and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

15. APPENDICES

15.1. World Health Organization Classification of Acute Myeloid Leukemia

Acute myeloid leukemia with recurrent genetic abnormalities

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

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasma

Acute myeloid leukemia, not otherwise categorized

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

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

15.2. Myelodysplastic Syndromes World Health Organization Classification System

Myelodysplastic Syndromes World Health Organization Classification System		
Category	**Definition**	
	Peripheral Blood Smear Evaluation	**Bone Marrow Evaluation**
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia[a] No or rare blasts (< 1%)	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ringed sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with Multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)[b] No Auer rods < $1x10^9$/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ± 15% ringed sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts[b] No Auer rods < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts[b] No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s)[c] 5%-19% blasts Auer rods[c] < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts[c] Auer rods ±[c]
Myelodysplastic syndrome - unclassified (MDS-U)	Cytopenias < 1% blasts[b]	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS <5% blasts
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

[a] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

[b] If the marrow myeloblast percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.

Myelodysplastic Syndromes World Health Organization Classification System (Continued)

[c] Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other 2 findings, Auer rods + and/or 5% to 19% blasts in the blood.

[d] Includes unbalanced abnormalities -7 or del(7q), -5 or del(5q), i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13), balanced abnormalities t(11;16)(q23;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.1), t(2;11)(p21;q23), inv(3)(q21q26.2), and t(6;9)(p23;q34), and complex karyotype (3 or more chromosomal abnormalities) involving one of more of the listed abnormalities.

Sources:

Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute myeloid leukemia: rationale and important changes. Blood 2009; 114(5):937-51.

15.3. International Prognostic Scoring System Score for Myelodysplastic Syndromes

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics[1]	Very Good	—[3]	Good	—[3]	Intermediate	Poor	Very Poor
BM blast, %	≤ 2	—[3]	> 2%- < 5%	—[3]	5%-10%	> 10%	—[3]
Hemoglobin	≥ 10	—[3]	8- < 10	< 8	—[3]	—[3]	—[3]
Platelets	≥ 100	50-< 100	< 50	—[3]	—[3]	—[3]	—[3]
ANC	≥ 0.8	< 0.8	—[3]	—[3]	—[3]	—[3]	—[3]

[1] Very good: −Y, del(11q); Good: Normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones; Poor: −7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities; Very poor: Complex: > 3 abnormalities

[2] Not applicable.

Note- Scores for risk groups are as follows: Very low: ≤ 1.5; Low: > 1.5-3; Intermediate:> 3-4.5; High: > 4.5-6; Very high: > 6

Sources:

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood.* 2012;120(12):2454-65.

15.4. Risk Status Based on Validated Cytogenetics and Molecular Abnormalities

Risk Status	Cytogenetics Abnormalities	Molecular Abnormalities
Favorable-risk	Core binding factor: inv(16)[1, 2] **or** t(16;16)[1] **or** t(8;21)[1] t(15;17)	Normal Cytogenetics: NPM1 mutation in the absence of FLT3-ITD **or** isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	inv(16), t(16;16), t(8;21) : with c-KIT [3] 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)[4]	Normal Cytogenetics: with FLT3-ITD [5] mutation

* The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories.

[1] Other cytogenetics abnormalities in addition to these finding do not alter risk status

[2] Paschka P, et al. . Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML Study Group (AMLSG). Blood 2013;121:170-177

[3] Emerging data indicate that the presence of c-KIT mutations in patients with t(8;21) and to a lesser extent inv(16) confers a higher risk of relapse.

[4] Philadelphia+ AML t(9;22) consider managing as myeloid blast crisis in CML. These subjects are excluded from study entry.

[5] FLT3-IDT mutations are considered to confer a significant poorer outcome in patients with normal karyotype. There is controversy as to whether FLT#-TDK mutation carry an equal poor prognosis.

Source: National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Acute Myeloid Leukemia Version 1.2015. National Comprehensive Cancer Network website. Available at https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf Accessed 20Apr2015.

15.6. New York Heart Association Classification

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

15.7. National Cancer Institute Common Terminology Criteria for Adverse Events

The NCI CTCAE, Version 4.03, can be accessed using the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

15.8. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI:

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, and the 41st WMA General Assembly, Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added); 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added); and 59th WMA General Assembly, Seoul, October 2008.

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the subject's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the Sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor

ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on subjects or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent,

preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious subjects, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the subjects who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the subjects who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, subjects entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study or the subject's decision to withdraw from the study must never interfere with the subject-physician relationship.

35. In the treatment of a subject, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the subject or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

15.9. CYP Sensitive Substrates

From FDA DDI Website: Table 7. Examples (1) of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range (7/28/2011)		
CYP Enzymes	**Sensitive substrates (2)**	**Substrates with narrow therapeutic range (3)**
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6 (4)	Bupropion, efavirenz	
CYP2C8	Repaglinide(5)	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A(6)	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,(7) cisapride,(7) cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(7)
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, Venlafaxine	Thioridazine

(1) 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.
(2) *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.
(3) CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
(4) The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.
(5) Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.
(6) Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
(7) Withdrawn from the United States market because of safety reasons.

15.10. Transporter Sensitive Substrates

From the FDA DDI Website: Table 13. Examples of In Vivo Substrates for Selected Transporters (1) (7/28/2011)

Transporter	Gene	Substrate
P-gp	ABCB1	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	ABCG2	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan
OATP1B1	SLCO1B1	Atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38 (active metabolite of irinotecan), rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan
OATP1B3	SLCO1B3	Atorvastatin, rosuvastatin, pitavastatin, telmisartan,(2) valsartan, olmesartan
OCT2	SLC22A2	Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin
OAT1	SLC22A6	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	SLC22A8	Acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin, rosuvastatin, sitagliptin

(1) 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.

(2) Selective for OATP1B3.

15.11. 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 up includes:
  - 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

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UserName: Brownstein, Carrie (cbrownstein)
Title: VP, Clin R&D Myeloid
Date: Tuesday, 17 October 2017, 05:33 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. **Update to the end of study definition**

   Based on a regulatory request safety will be followed for 3 years from the first dose of the last subject enrolled into Phase 2.

   - "3 years after the first dose of the last subject enrolled into Phase 2"
   - "All subjects are to be followed for survival status follow up every 3 months until death, withdrawal of consent, or end of study for survival."

   Revised Sections: 2, 7.1.4, 8.5, 9.9.2, 12.5.7

2. **To reduce the visit and assessment burden for ongoing study subjects including those on treatment and those in long term follow up.**

   As global regulatory submission are ongoing and final data for primary efficacy analysis have been collected, the rigorous visit and assessment schedule has been modified. All subjects will be contacted monthly for the status of the subject and safety follow up and visits to the site will be quarterly, and efficacy assessments (including bone marrow biopsies, bone marrow aspirates, and peripheral blood) will be performed based on each individual subject response to study treatment.

   Revised Sections: 2, 7.1.4, 8.5, 9.6, 9.9.1, 10.1, Table 2 (Cycle 3-Cycle 12, Cycle 13 and beyond, Safety Follow-up visits, Footnotes; 5, 19, 29, 31, 32, 33), Table 3 (Cycle 3-Cycle 12, Cycle 13 and beyond, Safety Follow-up visits, Footnotes; 3, 18, 27, 29, 30, 31), Table 4 (Cycle 4-Cycle12), Table 5 (Cycle 3), 10.6.1, 10.6.2, 10.6.3, 10.6.4, 10.6.5, 10.7, 10.8.1, 10.8.2, 10.9.1, 10.10.2, 10.11

Minor changes included in this amendment are summarized below:

- Updated contact details for the responsible medical officer's medical monitor for the AG221-C-001 study.

  Revised Sections: Responsible Medical Officers and Medical Monitor Contact Information

- While considered an exploratory objective and endpoint, α-KG levels have not been routinely tested as an ongoing analysis but still may be analyzed on an exploratory basis.

  Revised Sections: 12.5.6

- Text has been updated to align the protocol and SAP in the following sections.
  - "The data with the cutoffs of 15 Apr 2016 and 14 Oct 2016 were analyzed to descriptively estimate the efficacy and safety profile of AG-221 for the NDA submission and 4-month safety update. These interim analyses were not intended to modify the study conduct."
  - "The study data will be analyzed and reported based on all subjects' data from the dose escalation and expansion phases up to the time when all subjects have completed at least 6 cycles of treatment regardless of dose interruption or discontinued study drug earlier, or when the follow up is deemed adequate for the

assessment of duration of response, whichever is the later date. Any additional data for subjects continuing to receive study treatment or in follow up for HSCT or survival past the data cutoff date for the clinical study report (CSR) will be reported in a final descriptive update at the end of study."

Revised Sections: 2, 12.4, 12.5.1, 12.5.7

- Safety and efficacy data have been updated to align the protocol with the IB and reflect management of the updated important events.

  Revised Sections: 5.2.2.5, 5.2.3, 9.8, 9.8.1, 9.8.2, 9.8.3, 9.8.4, 9.8.5, 9.8.6

- Descriptions of drug strength and packaging have been clarified to reflect the current status of drug at the site.

  Revised Sections: 9.1, 9.2

- Though not considered an "Important Event" (Section 9.8), guidance for the monitoring of liver function was added to the appendices.

  Revised Sections: 15.11

1. JUSTIFICATION FOR AMENDMENT

The justifications for the major changes included in Amendment 6 (Protocol Version 7.0, dated 13 Oct 2015) relative to Amendment 5, Protocol Version 6.0 (dated 18 May 2015) are listed below and detailed in the pages that follow.

This amendment to the protocol has been developed based on feedback received from the Food and Drug Administration regulatory authority. The purpose of this amendment is to clarify, in the Phase 2 portion of the trial, the inclusion of patients with an unmet medical need defined as:

- Diagnosis of AML according to World Health Organization criteria and disease relapsed or refractory as defined by:
- Subjects who relapse after allogeneic transplantation;
- Subjects in second or later relapse;
- Subjects who are refractory to initial induction or reinduction treatment;
- Subjects who relapse within 1 year of initial treatment, excluding patients with favorable-risk status according to NCCN Guidelines (NCCN 2015). Favorable-risk cytogenetics: inv(16), +(16;16), t(8;21), t(15;17).

  Impacted sections are: Section 2.0-Synopsis; Section 7.1-Figure 7; Section 7.1.3-Overview of Phase 2; and Section 8.2-Inclusion Criteria-Inclusion Criterion #2

In addition to the above mentioned modification, the following changes were implemented:

- Clarification of the type of sample needed for central testing for IDH2 mutation. Bone marrow biopsy was erroneously added to the previous version of the protocol. For subjects in the Phase 2 portion of the trial, central testing of IDH2 mutation of bone marrow aspirate and peripheral blood is required during screening to confirm eligibility.

  Impacted sections are: Section 2.0-Synopis; Section 7.1.3-Overview of Phase 2; Section 8.2-Inclusion Criteria-Inclusion Criterion #3; Section 10- Schedule of Event; and Section 10.7-Bone Marrow Samples and Peripheral Blood Leukemic Blast Cells

- Added guidance for treatment of Differentiation-like Syndrome in cases in which subject is affected by infections requiring hospitalization, particularly those with pulmonary or pericardial manifestations, that do not respond to anti-infective treatments or worsen within the first 48 hours.

  Impacted section is: Section 9.8.2.- Differentiation-like Syndrome

- Clarification of the criteria for intra-subject dose escalation and modification in patients enrolled in the Phase 2 portion of the trial. Language was modified to ensure consistency across protocols in the program.

  Impacted sections is: Section 9.7.2-Intra-Subject Dose Modification Criteria

- Modification of language to increase the required duration of abstinence from sexual intercourse or use of two highly effective forms of contraception following the last dose of AG-221. Duration was increased from 90 to 120 days post-AG-221.

Impacted sections are: Section 2.0-Synopis ; Section 8.5-Subject Withdrawal Criteria and Replacement of Subjects; Section 8.2-Inclusion Criteria-Inclusion Criterion #12; and Section 11.3-Pregnancy Reporting

- Removal of clinical data from ongoing trial to ensure consistency with data included in the investigator brochure (IB).

  Impacted section is: Section 5.2.3-Emerging Clinical Data

Throughout the protocol

The amendment also includes several other minor clarifications and corrections:

- Clarification about requirement for RBC and platelets transfusions
- Updates around role of medical monitor in decision regarding administration of concomitant medicines.
- Clarification of PK sampling time points
- Clarification of definition of Relapse (Table 9)
- Clarification of definition of Disease Progression (Table 10)
- Addition of NCCN 2015 reference

Furthermore, the amendment includes typographical and formatting corrections and other minor editorial changes that did not affect the scope or conduct of the trial and that were carried out to improve readability.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Section Number	Section Title(s)	Description of Change(s)
NA	Title Page Study Sponsor	Modified the study sponsor to Celgene Corporation, Summit, NJ. The study will be conducted in collaboration with Agios Pharmaceuticals, Cambridge, MA
NA	Title Page-Title	Updated Title to reflect addition of Phase 2 (previously referred as Part 2 Expansion)
NA	Title Page Responsible Medical Officer	Included Celgene Corporation Responsible Medical Officer and Updated Agios Pharmaceuticals Responsible Medical Officer
2.0	Synopsis -Number of Subjects (planned)	Updated Overall Sample Size to reflect current number of subjects enrolled in the study.
7.1.4	General Conduct	
8.1	Number of Subjects	
12.1	Sample Size Estimation	
5.2.3	Emerging Clinical Data	Update clinical data from ongoing trial
2.0	Synopsis -Number of Subjects (planned)	Clarification of Primary Efficacy Population to include Full Analysis Set defined as all subjects enrolled and received at least one dose of study treatment.
12.2	Populations for Analysis	
12.5.7	Clinical Activity Analyses	
2.0	Synopsis	Clarification of Study Objectives and Endpoints to reflect difference in design of the Phase 1 and Phase 2 portion of the study
6.0	Trial Objectives and Endpoints	
12.5.7	Clinical Activity Analyses	
2.0	Synopsis	Clarification of Study Design and addition of Study Diagram (7.1. only) to reflect difference in design of the Phase 1 and Phase 2 portion of the study.
7.1	Overall Study Design	
2.0	Synopsis - Investigational product, dosage and mode of administration	Clarified rationale for selection of 100 mg QD as starting dose for Phase 1 Part 1 Expansion and Phase 2 .
7.1.2	Overview of Phase 1/Par 1 Expansion	
7.1.3	Overview of Phase 2	
7.3.2	Rationale for the Dose Selected	
2.0	Synopsis	Updated Eligibility Criterion #2 to provide additional clarification on the definition of the disease under evaluation in this study
7.1.1	Overview of the Dose Escalation Phase	
8.2	Inclusion Criteria	
2.0	Synopsis	Addition of Inclusion Criterion #13
8.2	Inclusion Criteria	

Section Number	Section Title(s)	Description of Change(s)
2.0	Synopsis	Addition of Exclusion Criterion #22: Subjects who have previously received treatment with an inhibitor of IDH
8.3	Exclusion Criteria	
8.4	Subject Identification and Registration	Addition of Interactive Response Technology
8.5	Subject Withdrawal Criteria and Replacement of Subjects	Added language to clarify distinction between discontinuation from study treatment and discontinuation from the study.
9.7.3	Dose Discontinuation Criteria	
9.5	Clinical Supply	Clarification of Investigator responsibility regarding inventory of study treatment.
9.7.2	Intra-subject Dose Modification Criteria	Clarification on Dose Modification Guidance to include guidance for dose escalation, dose reduction, and dose discontinuation.
9.12.3	Restricted Concomitant Therapy	Clarification of co-administration of restricted concomitant therapy.
2.0	Synopsis	Clarified Follow-up and Survival Follow-up Time points for all subjects.
7.1.4	General Conduct	
8.5	Subject Withdrawal Criteria and Replacement of Subjects	
9.9.1	Treatment Duration	
9.9.2	End of Study	
10.1	Schedule of Events	
10.8	Clinical Activity Assessments	
10.1	Schedule of Events	Updated time points for Pregnancy Testing, and Transfusion Assessment
10.1	Schedule of Events	Updated time points in Phase 2 to evaluate PK in the QD schedule.
10.9	Pharmacokinetic Assessments	
10.3	Information to be collected on Screening failures	Added Celgene template language
10.4	Demographic Data and Medical, Surgical, and Medication History	Clarification of data needed
2.0	Synopsis	Modification of standard assessment criteria based on the response pattern seen with AG-221 mechanism of action
10.8.3	Assessments of Response Criteria	
15.1	World Health Organization Classification of Acute Myeloid Leukemia	Appendices added to improve clarity of the protocol.
15.2	Myelodysplastic Syndromes World Health Organization Classification System	
15.3	International Prognostic Scoring System Score for Myelodysplastic Syndromes	

Section Number	Section Title(s)	Description of Change(s)
15.4	Risk Status Based on Validated Cytogenetics and Molecular Abnormalities	

The amendment also includes typographical and formatting corrections, and other minor editorial changes, which did not affect the scope or conduct of the trial and that were carried out to improved readability of the protocol.

PROTOCOL AG221-C-001

AMENDMENT 4 SUMMARY OF CHANGES

A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-221 in Subjects with Advanced Hematologic Malignancies with an IDH2 Mutation

The major changes included in Amendment 4 (Protocol Version 5.0, dated 02 February 2015) relative to Amendment 3, Protocol Version 4.0 (dated 16 April 2014) are itemized below and detailed in the pages that follow:

- Added a Part 2 to the expansion phase of the study to include enrollment of an additional 125 subjects with relapsed or refractory acute myelogenous leukemia (AML), including detailed information on inclusion criteria and study procedures. Data from these subjects will be used to confirm the clinical activity, safety, and pharmacokinetic/pharmacodynamic (PK/PD) profile of AG-221 for the treatment of subjects with relapsed or refractory AML that harbor an isocitrate dehydrogenase-2 (IDH2) mutation.
  - Subjects in this phase of the expansion are required to have central laboratory confirmation of IDH2-mutated disease prior to treatment with AG-221.
  - Subjects in Part 2 expansion will undergo more limited PK/PD evaluations than those in the dose escalation phase or Part 1 of the expansion phase and will have time-matched triplicate electrocardiograms (ECGs) performed, and are not required to have evaluations for plasma cholesterol and 4β-OH-cholesterol levels.
  - Disease response assessments, including bone marrow biopsy and peripheral blood, are to be conducted more frequently in subjects in Part 2 of the expansion phase (every 28 days after Day 57 rather than every 56 days) through Month 12 in this cohort.
  - Disease response information for subjects in Part 2 of the expansion phase will be evaluated by an Independent Review Committee (IRC).
  - Information on red blood cell and platelet transfusions will be captured for subjects in Part 2 of the expansion phase, including dates of the transfusion and units administered, as well as the associated hemoglobin levels, for the 8-week period prior to first dose of study drug and during the treatment period.
- Based on the differences in the assessments to be conducted for subjects in Part 2 of the expansion phase, a new schedule of assessments was added for these subjects.
- Based on the differences in PK/PD and ECG assessments across the cohorts, 2 new tables of PK/PD and ECG assessments were added to clarify assessments for subjects in the dose escalation phase and Part 1 of the expansion phase versus Part 2 of the expansion phase.
- Statistical methodology was updated to include endpoints and statistical considerations for data from Part 2 of the expansion phase.

- Updated the number of subjects to be enrolled and study sites to be included based on the additional Part 2 expansion arm.
- Modified the study sponsor to Celgene Corporation, Summit, NJ. The study will be conducted in collaboration with Agios Pharmaceuticals, Cambridge, MA.
- Updated information on emerging clinical data from the trial, including safety, PK/PD and clinical activity data available from the first 73 subjects.
- Added screening assessment to include an evaluation of uridine diphosphate-glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) gene mutation.
- Modified the definition of hematologic dose-limiting toxicity (DLT) to exclude ≥Grade 1 blood bilirubin increases in subjects with a UGT1A1 mutation. In subjects with a UGT1A1 mutation, blood bilirubin increases of >5× upper limit of normal (ULN) may be considered a DLT.
- Modified the exclusion criterion related to elevated bilirubin levels to allow for higher elevations in subjects with UGT1A1 mutation following approval by the Medical Monitor.
- Added an evaluation of the effect of food on the PK of AG-221 for a subset of subjects in the dose escalation phase.
- Provided for subjects who achieve an adequate response to treatment with AG-221 who then proceed to hematopoietic stem cell transplant (HSCT) off treatment to be followed for outcome to support the overall clinical benefit of AG-221 in this setting. Subjects who subsequently relapse after HSCT may be eligible to restart treatment with AG-221 with Medical Monitor approval.
- Modified requirements for clinical laboratory evaluations:
  - Removed the requirement for urinalysis for all subjects as to date there have been no safety findings related to urinalysis during dose escalation at doses up to 200 mg/day.
  - Added a requirement for urine pregnancy tests on day 1 of each treatment cycle.
  - Added bicarbonate assessment to chemistry
  - Added a lipid panel to be conducted at screening, every 6 months on treatment and at end of treatment.
- Clarified that response criteria other than the International Working Group (IWG) response criteria for AML or myelodysplastic syndrome (MDS) would be used for subjects with other hematologic malignancies enrolled in Part 1 expansion, Arm 3.
- Added definitions for stable disease and progressive disease for subjects with AML as these specific response definitions are not included in the IWG response criteria.
- Added an assessment of survival status monthly after completion of the Day +28 followup visit and for the collection of new antineoplastic therapies after treatment with AG-221.
- Removed the requirement that treatment with hydroxyurea be administered only during the first 28 days of treatment with AG-221.
- Added additional tablet strengths of AG-221 (25, 100 and 150 mg).

- Added an allowance for subjects who experience disease progression per the applicable response criteria who are, in the opinion of the Investigator, benefiting from treatment, to be allowed to continue on study drug with approval of the Medical Monitor.
- Added guidelines for the management of subjects who experience adverse events of special interest, including QT prolongation and differentiation-like syndrome.
- Provided more detailed information on pregnancy reporting requirements and the specific use of contraceptives.

In addition to the above, minor wording changes and clarifications were made that are not reflected in this document.

PROTOCOL AG221-C-001

AMENDMENT 3 SUMMARY OF CHANGES

A Phase 1, Multicenter, Open-Label, Dose-Escalation, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-221 in Subjects with Advanced Hematologic Malignancies with an IDH2 Mutation

The major changes included in Amendment 3 (Protocol Version 4.0, dated 16 April 2014) relative to Amendment 1, Protocol Version 2.0 (dated 18 July 2013) are itemized below and detailed in the pages that follow:

- Added information on emerging clinical data from the trial, including safety, PK/PD and clinical activity data available from the first 22 subjects.
- Added information that a once daily dosing regimen has been explored based on the emerging PK/PD data.
- Provided detailed information, including inclusion criteria, for the expansion cohorts. Four expansion arms are planned, with 25 subjects per arm, in specific hematologic malignancy subsets.
- Updated the number of subjects and study sites to be enrolled based on the emerging data and the expansion cohorts.
- Added evaluation of α-ketoglutarate as a potential biomarker and plasma cholesterol and 4β-OH-cholesterol levels as a potential cytochrome (CYP) 3A4 induction marker.
- Added evaluation of PK/PD on Day -3 for initial 15 subjects in each expansion arm; unless omitted by Medical Monitor.
- Included additional samples for PK/PD assessments.
- Added specific AML response criteria (Cheson, 2003) for evaluation of clinical activity. Modified peripheral blood sampling for evaluation of response to every 28 days.
- For the adequate renal function inclusion criterion, added the option of using creatinine clearance based on the Cockroft-Gault equation or serum creatinine.
- Deleted the requirement for bone marrow biopsy when a core biopsy is unobtainable and/or is not part of the standard of care; bone marrow aspirates are required. A bone marrow biopsy is required in case of dry tap or failure (mainly dilution) with the aspiration.
- Deleted the exclusion criterion for subjects who had previously received study drug treatment under this protocol; clarified that subjects who had previously been treated and had undergone hematopoietic stem cell transplant with subsequent relapse could re-enter the study with Medical Monitor approval.

- Clarified the exclusion criterion for QTc interval for subjects with right bundle branch block.
- Added an exclusion criterion for patients with active Hepatitis B.
- Included information on the potential for phototoxicity with specific warnings to subjects regarding protection from sun exposure.
- Included recommendation to avoid the use of antacids, H1 blockers, or proton pump inhibitors while taking AG-221. Given the solubility profile of AG-221, the exposure can be much lower for patients with elevated gastric pH.
- Updated the statistical analysis plan to reflect the increased sample size for the expansion cohorts and to add detail on analysis of clinical activity.

In addition to the above, minor administrative changes were made.

PROTOCOL AG221-C-001

AMENDMENT 2 (FRANCE) SUMMARY OF CHANGES

A Phase 1, Multicenter, Open-Label, Dose-Escalation, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-221 in Subjects with Advanced Hematologic Malignancies with an IDH2 Mutation

The major changes included in Amendment 2 (Protocol Version 3.0, dated 23 September 2013) relative to Amendment 1, Protocol Version 2.0 (dated 18 July 2013) are itemized below and detailed in the pages that follow:

- Deleted the requirement for bone marrow biopsy when a core biopsy is unobtainable and/or is not part of the standard of care; bone marrow aspirates are required. A bone marrow biopsy is required in case of dry tap or failure (mainly dilution) with the aspiration.
- For the adequate renal function inclusion criterion, added the option of using creatinine clearance based on the Cockroft-Gault equation or serum creatinine.
- Added an exclusion criterion for patients with active Hepatitis B.
- Included information on the potential for phototoxicity with specific warnings to subjects regarding protection from sun exposure.

In addition to the above, minor administrative changes were made; these are also detailed in the pages that follow.

PROTOCOL AG221-C-001

AMENDMENT 1 SUMMARY OF CHANGES

A Phase 1, Multicenter, Open-Label, Dose-Escalation, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-221 in Subjects with Advanced Hematologic Malignancies with an IDH2 Mutation

The major changes included in Amendment 1 (Protocol Version 2.0, dated 18 July 2013) relative to the original protocol (dated 3 June 2013) are itemized below and detailed in the pages that follow:

- Modified the inclusion criterion for subjects with myelodysplastic syndrome to indicate that patients must not be candidates for regimens known to provide clinical benefit.
- Broadened the definition of non-hematologic toxicities to include any clinically significant events ≥Grade 3 in severity.
- Clarified the text regarding dose escalation to indicate that escalation is never to exceed 100%.
- Added assessments of creatinine kinase, cardiac troponin, amylase and lipase at screening, Day -3 (for subjects undergoing 72-hour PK/PD profile), on Day 1 of each treatment cycle, and at the End of Treatment visit.

In addition to the above, minor administrative changes were made; these are also detailed in the pages that follow.