STATISTICAL ANALYSIS PLAN

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 DRUG: **AG-221**

PROTOCOL NUMBER: **AG-221-C-001**

DATE FINAL: **04 Oct 2019**

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Statistical Therapeutic Area Head

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

2-HG	2-hydroxyglutarate
α-KG	Alpha-ketoglutarate
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	Baseline
BMI	Body mass index
BMT	Bone marrow transplant
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
C#D#	Cycle <*number*>, Day <*number*>
CI	Confidence interval
CR	Complete response
CRh	CR with incomplete hematologic recovery (CRh)
CRi	CR with incomplete neutrophil recovery
CRp	CR with incomplete platelet recovery
CRP	C-reactive protein
CRR	Complete response rate
CSR	Clinical study report
DBP	Diastolic blood pressure
DDS	Dose determining set
DLT	Dose-limiting toxicity
DOCR	Duration of complete response
DOR	Duration of response
EAS	Evaluable analysis set
ECG	Electrocardiogram

[redacted]

ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
eCRF	Electronic case report form
EFS	Event-free survival
FAS	Full analysis set
HCO3	Bicarbonate
HDL-C	High-density lipoprotein cholesterol
HSCT	Hematopoietic stem cell transplant
ICSH	International Council for Standardization in Hematology
IDH2	Isocitrate dehydrogenase protein 2
INR	International normalized ratio
IRAC	Independent Response Adjudication Committee
IWG	International Working Group
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
MAD	Maximum administered dose
mCR	Marrow CR
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic
PK	Pharmacokinetic
PR	Partial response
PS	Performance status
PT	Preferred term
RBC	Red blood cell (count)

[redacted]

RP2D	Recommended Phase 2 dose
R/R	Relapsed or refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SBP	Systolic blood pressure
SCS	Summary of Clinical Safety
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TI	Transfusion independence
TTBR	Time to best response
TTCR	Time to complete response
TTR	Time to response
WBC	White blood cell (count)
WHO	World Health Organization

[redacted]

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objectives of Phase 1 dose escalation/Part 1 Expansion are:

- 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 the maximum tolerated dose (MTD) or maximum administered dose (MAD) and/or the recommended Phase 2 dose (RP2D) of AG-221 in subjects with advanced hematologic malignancies.

The primary objective of Phase 2 is:

- To assess the efficacy of AG-221 as treatment for subjects with relapsed or refractory (R/R) acute myelogenous leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation.

3.2. Secondary Objectives

The secondary objectives of Phase 1 dose escalation/Part 1 Expansion are:

- 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.

The secondary objectives of Phase 2 are:

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

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 1/2, multicenter, open-label, 3-part (Phase 1 dose escalation, 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. The study includes a dose escalation phase to determine MTD /MAD and/or RP2D; an expansion phase (Part 1 Expansion) to further evaluate the safety, tolerability, and clinical activity of AG-221; and a Phase 2 portion to assess the clinical efficacy of AG-221 at the RP2D and to further evaluate safety in subjects with R/R AML carrying an IDH2 mutation.

The dose escalation phase of the study will be conducted in up to 5 subjects per dose level; with the exception that the MTD/MAD requires 6 subjects. Additional subjects may be needed during dose escalation (for the replacement of subjects who are not evaluable for PK/PD, safety, clinical activity and for evaluation of alternative dosing regimens other than the planned escalation scheme or the MTD/MAD) to optimize the RP2D and regimen(s).

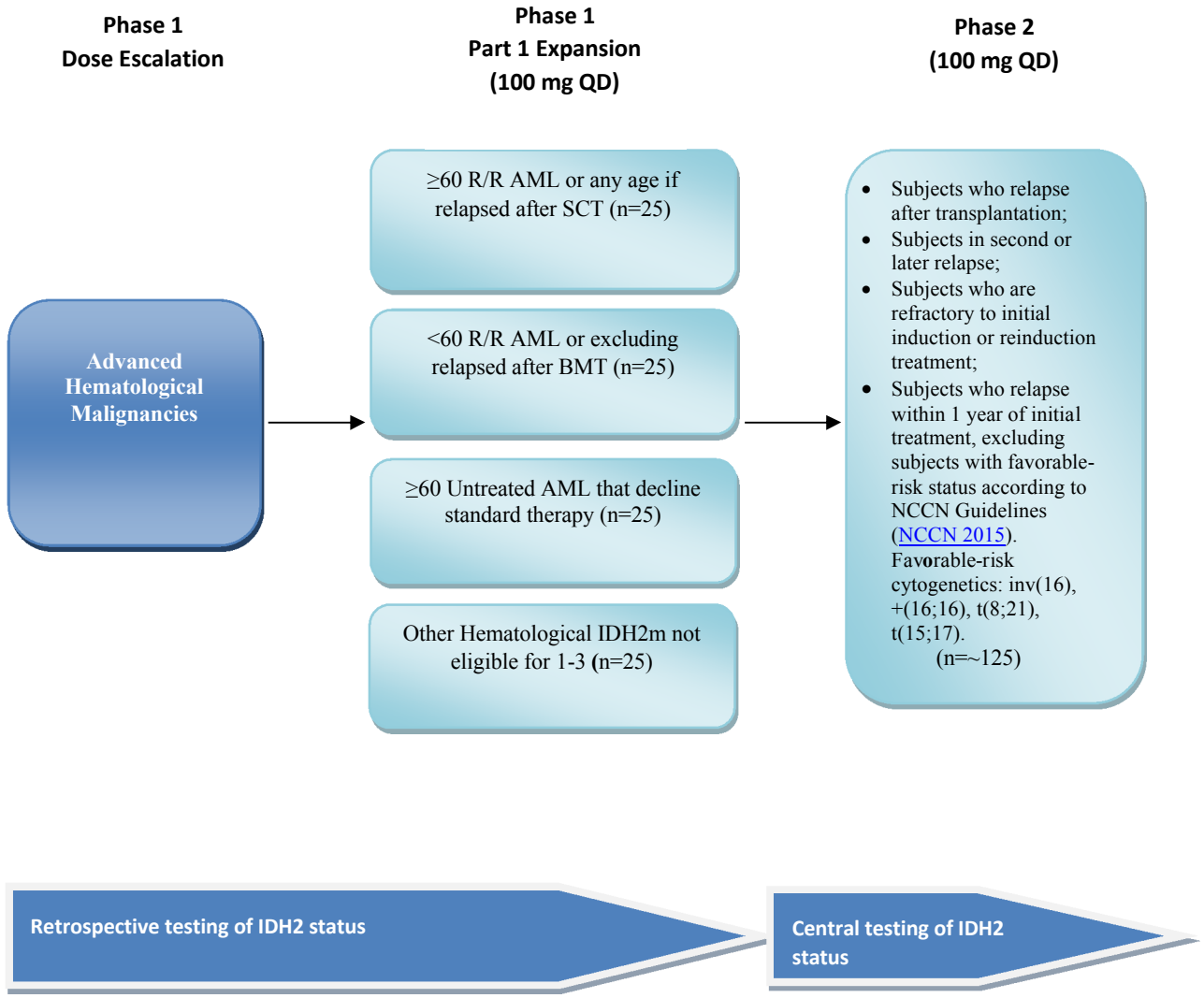
The Part 1 Expansion will enroll 4 cohorts, each comprised of a minimum of 25 subjects in specific hematologic malignancy subsets (a minimum of 100 subjects).

The Phase 2 portion will enroll a cohort of approximately 125 subjects with R/R AML.

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.

[redacted]

Figure 1: Study Diagram

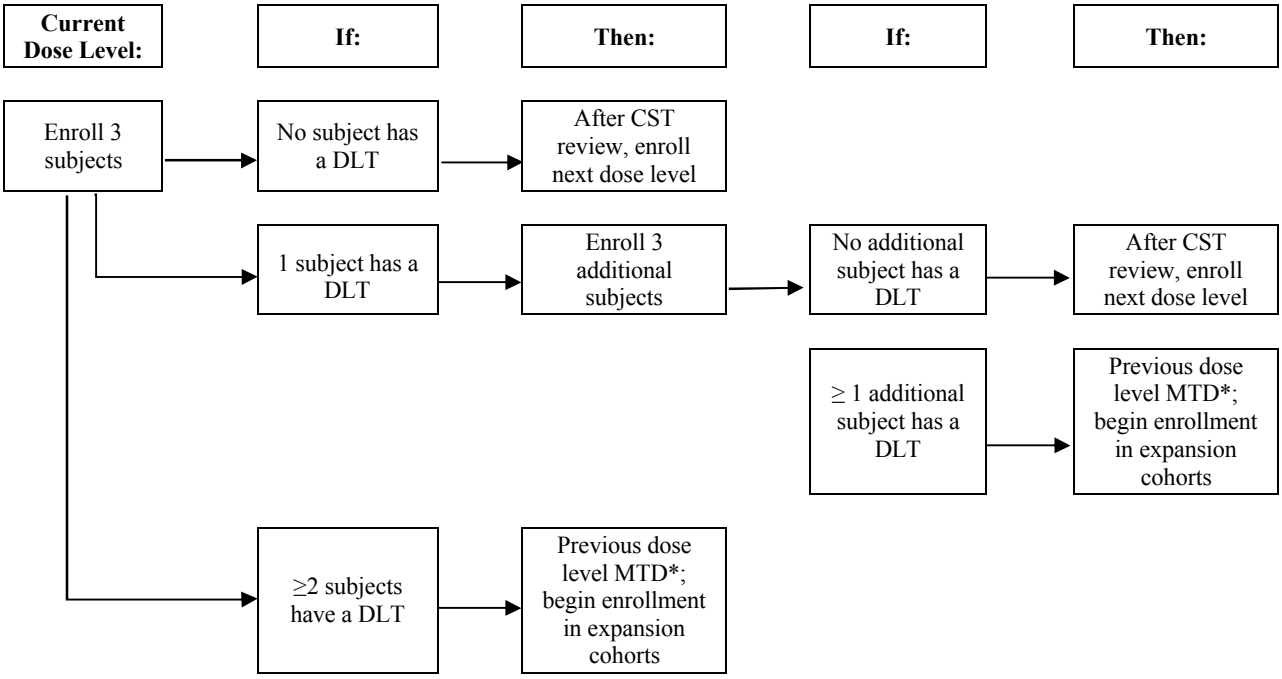


Note: Part 1 Expansion and Phase 2 at 100 mg QD will proceed in parallel as soon as this dose is declared safe during the dose escalation portion of the study.

4.1.1. Overview of the Phase 1/Dose Escalation Phase

A schematic of the dose escalation scheme is provided in Figure 2. 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 initial dosing regimen was twice daily (BID) (approximately every 12 hours). Based on the emerging data, a once daily (QD) dosing schedule was implemented. Alternative dosing schedules (eg, loading dose followed by QD 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.

Figure 2: 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 experience a DLT at this dose.
Note: CST = Clinical Study Team; DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

The planned study drug doses for the dose escalation phase are summarized in Table 2. The starting dose for this study was 30 mg administered approximately every 12 hours, based on the results of GLP dose range-finding toxicology studies. Based on evaluation of the safety, tolerability, and PK/PD data of the previous dose levels, an intermediate dose level not specified in the tables below may also be explored. The MAD of AG-221 in this portion of the trial is 650 mg administered orally QD.

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.

Table 2: 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 Clinical Study Team reviewed the emerging safety data from each cohort to determine if dose escalation should occur. If after the third subject completed the 28-day DLT evaluation period (ie, Cycle 1) no DLTs were observed, the study proceeded with dose escalation to the next cohort. If 1 of 3 subjects experienced a DLT during the first cycle, 3 additional subjects were enrolled in that cohort. If none of the additional 3 subjects experienced a DLT (ie, DLTs occurred in <2 of 6 subjects), dose escalation continued to the next cohort. If 2 or more subjects in a cohort experienced DLTs during the first cycle, dose escalation would be halted and the next lower dose level would be declared the MTD. Alternatively, an intermediate dose level between the non-tolerated dose level and the previously tolerated dose level might be explored and declared the MTD if <2 out of 6 subjects experienced a DLT at that dose. If the MTD cohort included only 3 subjects, an additional 3 subjects would be enrolled at that dose level to confirm that <2 of 6 subjects experience a DLT at that dose.

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

Increases in the dose of AG-221 for each cohort were guided by an accelerated titration design, where the daily dose could be doubled (100% increase) from one cohort to the next until National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 2 or greater AG-221-related toxicity was observed in any subject within the cohort. Following evaluation of the event(s) by the Clinical Study Team, subsequent increases in dose were guided by the observed toxicity, and potentially PK and PK/PD data until the MTD was determined. The absolute percent increase in the daily dose was determined by the Clinical Study Team, predicated on the type and severity of any toxicity seen in the prior dose cohorts (but never exceeded 100%).

The MTD was the highest dose that caused DLT in <2 of 6 subjects.

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

Subjects who did not meet any of the treatment withdrawal criteria could continue treatment beyond Cycle 1.

4.1.2. Overview of Phase 1/Part 1 Expansion

A dose of 100 mg QD has been selected for initial evaluation in Part 1 Expansion. 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 a minimum of 100 subjects that are divided into 4 nonrandomized arms of a minimum of 25 subjects per arm with IDH2-mutated hematologic malignancies as follows:

- Arm 1: R/R AML and age ≥60 years, or any subject with AML regardless of age who has relapsed following a bone marrow transplant (BMT).
- Arm 2: R/R AML and age <60 years, excluding subjects with AML who have relapsed following a BMT.
- Arm 3: Untreated AML and age ≥60 years that declined 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.

4.1.3. 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 R/R AML with an IDH2 mutation.

The Phase 2 portion of the trial will enroll approximately 125 subjects with IDH2-mutated R/R AML defined as follows:

- 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 subjects with favorable-risk status according to National Comprehensive Cancer Network (NCCN)

Guidelines (NCCN v1.2015). Favorable-risk cytogenetics: inv(16), +(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 R/R AML with an IDH2 mutation.

Subjects in the Phase 2 portion of the trial are required to have IDH2 mutation testing performed by a central laboratory in samples of bone marrow aspirate and peripheral blood, and confirmed positive in bone marrow aspirate and/or peripheral blood during screening prior to study treatment.

4.2. Study Endpoints

4.2.1. Efficacy Measures and Endpoints

Response to treatment will be assessed by the site Investigator, using a modification of the 2003 International Working Group (IWG) criteria for AML (Cheson, et al. 2003) (Table 6 and Table 7). For subjects with malignancy type myelodysplastic syndromes (MDS), response to treatment will be assessed by the site Investigator using MDS modified IWG criteria (Cheson, et al. 2006) (Table 8).

Subjects who discontinue AG-221 treatment to receive a hematopoietic stem cell transplant (HSCT) will remain on study and be followed until documented disease progression or end of study.

Primary Endpoint:

Overall response rate (ORR): ORR is defined as the rate of complete response (CR), CR with incomplete neutrophil recovery (CRi), CR with incomplete platelet recovery (CRp), partial response (PR), and morphologic leukemia-free state (MLFS) for AML subjects and marrow CR (mCR) for MDS subjects.

Key Secondary Endpoints:

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

Rate of CR/CRh: Rate of CR and CRh where CRh is defined as a response of bone marrow blast <5% with absolute neutrophil count (ANC)> $0.5x10^9$/L and platelet >$50x10^9$/L.

Rate of complete response and complete response with incomplete hematological recovery (CR/CRi/CRp): Rate of CR, CRi, and CRp

Duration of response (DOR): Among subjects who have a response of CR, CRi, CRp, PR, or mCR (MLFS), DOR will be calculated from the date of the first occurrence of response to the date of documented disease relapse, progression or death, whichever is the earliest.

Overall survival (OS): Overall survival is defined as the time from first dose to the date of death.

56-Day transfusion independence (TI) rate: the rate of subjects who have been transfusion free for at least 56 consecutive days post baseline during treatment exposure period.

[redacted]

Other Secondary Endpoints:

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.

Duration of complete response (DOCR): Among subjects who have a best response of CR, DOCR will be calculated as the date of the first complete response to the date of documented disease relapse or death, whichever is earlier.

Duration of CR/CRh (DOCR/CRh): Among subjects who have a best response of CR or CRh, DOCR/CRh will be calculated as the date of the first CR or CRh to the date of documented disease relapse or death, whichever is earlier.

Time to response (TTR): Time to response will be assessed from the date of the first dose to the date of the first occurrence of any response, which includes CR, CRi, CRp, PR, and mCR/MLFS.

Time to Best Response (TTBR): Time to best response will be assessed from the date of the first dose to the date of the first occurrence of the best response.

Time to complete response (TTCR): Time to CR will be assessed from the date of the first dose to the date of the first CR.

Time to CR/CRh (TTCR/CRh): Time to CR/CRh will be assessed from the date of the first dose to the date of the first CR or CRh.

4.2.2. Safety Measures and Endpoints

Safety analyses will be performed separately for Phase 1 dose escalation, Part 1 expansion, the combined Phase 1, the Phase 2, and the combined Phase 1/2.

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 NCI CTCAE, version 4.03.
- Monitoring of safety laboratory parameters, physical examination findings, vital signs, 12-lead electrocardiograms (ECGs), evaluation of left ventricular ejection fraction (LVEF), and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

4.2.3. Pharmacokinetic and Pharmacodynamics Measures and Endpoints

The endpoints in pharmacokinetics (PK) and pharmacodynamics (PD) analyses will be detailed in the separate PK/PD analysis plan.

4.3. Stratification, Randomization, and Blinding

This is an open label, single-arm study with no randomization and stratification.

4.4. Sample Size Determination

Phase 1:

Based on the planned dose escalation scheme, it is estimated that a minimum of 166 subjects were to be enrolled in the Phase 1 part.

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, 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).

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.

Phase 2:

The Phase 2 phase will enroll approximately 125 subjects with R/R 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.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Tabulations will be produced for subject disposition, demographic and baseline disease characteristics, safety, and clinical activity parameters. The study data will be analyzed and reported for efficacy/safety when applicable based on all subjects' data from the Phase 1 dose escalation, the Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2 up to the data cut-off date of 29 July 2019.

Unless specified otherwise, the data will be presented as specified below:

1. In Phase 1 dose escalation, all subjects (combining different malignancy types [overall]) will be utilized. Data will be summarized by total daily dose groups, unless otherwise specified. The total daily dose is defined as the total dose a subject receives during a day based on the assigned or actual dose regimens for efficacy and safety, respectively.
2. In Part 1 Expansion, all subjects (combining different malignancy types) will be utilized and will be grouped into 4 arms (groups):
   - Arm 1: R/R AML and age ≥60 years, or any subject with AML regardless of age who has relapsed following a BMT.
   - Arm 2: R/R AML 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.
3. In the combined Phase 1, analyses will be presented by total daily dose groups as <100 mg, 100 mg and >100 mg for subjects with R/R AML. The overall subjects in the combined Phase 1 will be summarized by malignancy type including R/R AML, untreated AML, MDS, and other.
4. In Phase 2, data will be summarized primarily for all R/R AML subjects.
5. In the combined Phase 1/2, R/R AML will be presented by total daily dose groups as <100 mg, 100 mg and >100 mg, and the overall subjects will be presented by malignancy type.

For subjects who were discontinued from study treatment, underwent HSCT, and then re-restarted AG-221, data after restarting AG-221 will be excluded from all summary analyses except for death. The data collected after restarting AG-221 will be provided in listings.

Categorical variables will be summarized by frequency distributions (number and percentages of subjects) and continuous variables will be summarized by descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum, and maximum).

[redacted]

- Data from all study centers will be combined in the analysis.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999.'
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless otherwise specified.
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, SD, minimum, and maximum for continuous variables.
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form 'xx (xx.x)', where the percentage is in the parentheses.
- All analyses and summary tables will have the analysis population sample size for each treatment group in the column heading (ie, number of subjects).
- The day of the first dose of the study drug will be defined as study Day 1.
- For all analyses, unless noted otherwise, baseline will be defined as the most recent non-missing measurement by the first administration of study treatment. For subjects who receive the single dose on Day -3, baseline will be defined as the most recent measurement by the dosing on Day -3. For subjects who do not receive the single dose on Day -3, baseline will be defined as the most recent non-missing measurement by the first dose date.
- To summarize efficacy/safety data by visit, the post-baseline results will be summarized by the scheduled visit as appropriate.
- Calculation of Cycles:
  - The start date of each cycle will be determined based on scheduled study visit date for each subject, except for Cycle 1 which will use the first dose date of study drug as starting day. Once the start dates, eg, S_1, S_2, S_3… are determined, the end date of each cycle is calculated as the one day before the start date of the following cycle, ie, $E_i = S_{i+1} - 1$. The cycle number for each date of interest, eg, AE or study medication will be calculated based on event start date and the cycle window start and end dates. If an event date is on or after S_i and before S_{i+1}, the corresponding cycle number will be i. For the last cycle, the end date will be the last dose date, unless otherwise specified.

5.2. Analysis Populations

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

1. Full Analysis Set (FAS)
2. Safety Analysis Set (SAS)

[redacted]

3. Dose Determining Set (DDS)
4. Evaluable Analysis Set (EAS)

5.2.1. Full Analysis Set

Full Analysis Set (FAS): All subjects who received at least one dose of study treatment. The FAS is the primary analysis population for efficacy and will be the default analysis set for all analyses in each phase of study, unless otherwise specified. Subjects will be analyzed according to the treatment assigned.

5.2.2. Safety Analysis Set

Safety Analysis Set (SAS): All subjects who received at least 1 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 in each phase of study.

5.2.3. Dose Determining Set

Dose Determining Set (DDS): All subjects who take at least one dose of study drug in the dose escalation phase and either had a DLT during Cycle 1, regardless of amount of study drug exposure, or have no DLT and 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.

The DDS will be the default analysis set for the dose escalation phase for all MTD related analyses. Subjects will be analyzed according to the assigned dose group.

5.2.4. Evaluable Analysis Set

Evaluable Analysis Set (EAS): All subjects in the FAS for whom the baseline efficacy parameters (eg, hematologic and bone marrow assessments) and at least 1 post baseline response assessment at Day 28 or later are available and evaluable and who have experienced no major protocol violations. Sensitivity efficacy analyses will be produced using the EAS, if applicable. Subjects will be analyzed according to the assigned dose group. Major protocol violations leading to exclusion from EAS are defined as any of the following:

- Subject does not have an advanced hematologic malignancy.
- Subject does not have documented IDH2 gene-mutated disease.
- Subject received concomitant treatment for their malignancy other than AG-221.

[redacted]

6. SUBJECT DISPOSITION

The number of subjects treated, discontinued from treatment and study, along with the primary reason for discontinuation, will be summarized using frequency and percentage.

A summary of subject disposition will be presented separately for Phase 1 Dose Escalation by total daily dose, Part 1 Expansion by cohorts, and Phase 2 R/R AML, as described in items 1, 2, and 4 of Section 5.1, and for the FAS analysis set.

Disposition will also be analyzed for Phase 1 Dose Escalation by assigned dose group and overall for DDS.

Subject disposition for the combined Phase 1 will be presented by malignancy type for overall subjects and by <100 mg, 100 mg, and >100 mg for R/R AML as described in item 3 of Section 5.1 for the FAS analysis set.

Subject disposition for the combined Phase 1/2 will be presented by malignancy type for overall subjects and by <100 mg, 100 mg, and >100 mg and further by relapse/refractory status for R/R AML for the FAS analysis set.

Subjects screened and subjects treated by site will be summarized as described in items 1, 2, and 4 of Section 5.1. A separate summary tabulation will be presented by number of subjects and the reason of screen failures for Phase 1 and Phase 2.

A by-subject data listing will be provided for subjects with reasons for screening failure. Reasons for treatment discontinuation have been collected on the electronic case report form (eCRF) and will be summarized with the following categories:

- Withdrawal of consent
- Due to AE or DLT
- Any medical condition which, in the opinion of the Investigators, would put the subject at risk for continuing treatment
- Experiences disease progression
- Development of an intercurrent medical condition or need for concomitant treatment 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
- Protocol violation: non-adherence to study drug regimen or protocol requirements
- Lost to follow-up
- Pregnancy
- Death
- Bone Marrow Transplant
- Other

[redacted]

Reasons for not completing the study follow-up/study (ie, no more follow-up visits and no longer participating in the study) have been collected on the eCRF and will be summarized for all subjects with the following categories:

- Withdrawal of consent
- Lost to follow-up
- Death
- Other

Listings will be provided for discontinued subjects with reasons for treatment and study discontinuation displayed.

[redacted]

7. PROTOCOL DEVIATIONS/VIOLATIONS

Protocol deviations/violations were identified and assessed by the clinical research physician or designee following company standard operational procedure.

Protocol deviations and violations will be reviewed and finalized prior to database lock.

Protocol deviations and violations will be summarized separately for FAS using frequency tabulations and will be presented by subject groups as described in items 1, 2, and 4 of Section 5.1. Unlike other analyses, protocol deviations and violations analyses will be summarized for all subjects in Phase 2. Protocol deviations and violations will also be summarized for the combined Phase 1/2 R/R AML subjects following item 5 in Section 5.1.

A by-subject listing of all subjects with protocol deviations/violations will be provided. A separate listing of subjects with major protocol violations that lead to exclusion from the EAS will be provided.

[redacted]

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Unless specified otherwise, demographics and baseline disease characteristics will be summarized for Phase 1 dose escalation, Part 1 Expansion, and Phase 2 by subject groups as described in items 1, 2, and 4 of Section 5.1 for FAS. Phase 2 R/R AML subjects will be analyzed in EAS as well.

The Phase 1 dose escalation data will also be summarized by assigned dose groups in the DDS.

The combined Phase 1 and the combined Phase 1/2 will be analyzed in FAS and EAS as described in item 3 and 5 of Section 5.1 for subjects with R/R AML and overall subjects with different malignancy types. The demographics in the combined Phase 1/2 R/R AML subjects will be further summarized by refractory/relapse status in FAS.

Individual subject listings will be provided to support the summary tables.

8.1. Demographics

Age (years), height (cm), weight (kg), body mass index (BMI) (weight [kg]/height [m^2]), body surface area (BSA), and other continuous baseline characteristics will be summarized descriptively (number of subjects, mean, SD, median, minimum and maximum). Age category (<60, 60 - <70, 70 - <75, ≥75 years), sex, race, and ethnicity and other categorical variables will be summarized by frequency tabulations (count, percent).

Age will be calculated as follows: age = Integer ≤ [(ICF date– Date of Birth + 1) / 365.25].

Body mass index will be calculated as follows: BMI (kg/m^2) = weight in kg / (height in m)^2.

Body surface area will be calculated as follows: BSA (m^2) = weight $(kg)^{0.425}$ × height $(cm)^{0.725}/139.2$.

8.2. Baseline Disease Characteristics

The number and percentage of subjects in each of the following categories will be presented based on subject group structure described previously, when applicable. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum).

8.2.1. Baseline Disease Characteristics

1. ECOG PS at baseline (Grade 0, 1, 2, 3, or 4).
2. Gene mutation (IDH2) analysis at baseline (R140Q or R172K, or Unknown) (Local and Central).
3. UGT1A1 mutation status (heterozygous, homozygous, wild type, and NA).
4. R/R AML subtype (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 subjects with favorable-risk status according to National Comprehensive Cancer Network [NCCN] Guidelines [NCCN v1.2015]. Favorable-risk cytogenetics: inv(16), +(16;16),

[redacted]

t(8;21), t(15;17); subjects who have failed 2 or more cycles of first line therapy [consisting of an intermediate intensity chemotherapy, hypomethylating agent, or low dose cytarabine]).

5. Refractory/relapse status (primary refractory and relapse)
6. Prior systemic anti-cancer therapies for disease under investigation. (yes vs no).
7. Number of prior anti-cancer regimens (1, 2, 3, 4, and ≥5).
8. Prior stem cell transplants for AML (yes vs no); transplant type if yes (autologous, allogenic, other).
9. Cytogenetic risk status (favorable-risk, intermediate-risk, poor-risk, or failure).
10. Time (month) from last prior HSCT, calculated from starting date of prior HSCT to the first dose of AG-221.
11. Bone marrow blasts (%) and category (<20%; 20% to <30%; 30% to <50%; ≥50%) from the screening bone marrow aspirate/biopsy sample. Bone marrow aspirate will be used as the primary source. If no aspirate assessment is available, biopsy assessment will be used as default.
12. Peripheral blood blast (%).
13. Baseline values of the following lab parameters: Hemoglobin (<80 g/L, ≥80 g/L), platelet count (<50 $\times 10^9$/L, ≥50 $\times 10^9$/L), absolute neutrophil count (ANC) (<0.5 $\times 10^9$/L, 0.5 to <1 $\times 10^9$/L, ≥1.0 $\times 10^9$/L), white blood cells (WBC) (<15 $\times 10^9$/L, 15 to <30 $\times 10^9$/L, ≥30 $\times 10^9$/L), creatinine clearance (<45 mL/min, 45 to <60 mL/min, ≥60 mL/min). These lab parameters will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) as well.
14. Number of red blood cell (RBC) transfusions and number of units transfused and number of platelet transfusions and number of units transfused. Transfusion occurred within 4 weeks prior to and 4 weeks after the first dose is defined as the baseline and will be summarized for Phase 1; and transfusion occurred within 8 weeks prior to the first dose will be summarized for Phase 2.

A by-subject listing of the above baseline disease characteristics will be provided.

8.2.2. Underlying Malignancy Diagnosis

1. Malignancy type (R/R AML, untreated AML, MDS, or other).
2. If R/R AML, prior history of MDS (yes or no).
3. WHO classification of AML.
4. Time (month) from the initial diagnosis, calculated from time of initial diagnosis to date of first dose.

A by-subject listing of malignancy type will also be provided.

[redacted]

8.3. Medical/Surgical History and Concomitant Disease

Medical and surgical history, as well as concomitant disease, will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 by system organ class (SOC) and preferred term (PT). The summary will be produced for Phase 1 dose escalation, Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2 in FAS. Prior medical/history is defined as medical condition with a start date prior to start of study treatment. Concomitant disease is defined as an active disease that ended on or after the start of study treatment. They will be summarized separately.

8.4. Prior, Concomitant, and Post-Treatment Medications/Procedures

[redacted]

8.4.1. Prior/Concomitant/Post-treatment Medications

[redacted]

8.4.2. Concomitant/Post-Treatment Procedures

All concomitant/post-treatment procedures will be summarized in frequency tabulations (subject counts and percentages) and by SOC and PT.

[redacted]

8.4.3. Prior/Post-treatment Therapies for the Underlying Malignancy

This section includes therapies for the underlying malignancy including surgery, radiation, systemic or any other therapy, regardless of discontinuation date of treatment. In addition to the analyses elaborated below, listings for prior and post-treatment therapies for the underlying malignancy will be linked through a roadmap for each subject to facilitate subject-level review.

8.4.3.1. Surgeries

Post-treatment surgeries as documented on the designated CRF pages will be produced by SOC and PT and summarized in frequency tabulations.

A listing will be provided for post-treatment surgeries.

8.4.3.2. Radiation

The number and percentage of subjects who had any prior/post radiation therapy will be presented, if available. Summaries will include total frequency of subjects receiving any prior/post radiation therapy. For subjects with radiation therapy, treatment site, start/stop date, and dose will be presented in a listing.

8.4.3.3. Systemic Medication for the Underlying Disease

The number and percentage of subjects with any prior/post systemic medication for the underlying malignancy will be presented by ATC Classification. For subjects with systemic medication for the underlying malignancy, detailed information will be presented in a listing.

8.4.3.4. Stem Cell Transplants

The number and percentage of subjects with any on study stem cell transplants will be presented. Transplant by IDH2 mutation will be analyzed in the combined Phase 1, Phase 2, and the combined Phase 1/2 R/R AML subjects.

For subjects with stem cell transplants, type and date of procedure will be presented in a listing.

[redacted]

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Descriptive statistics will be used to summarize treatment duration, duration of treatment exposure, cumulative dose, average daily dose, dose intensity, relative dose intensity and dose modification. These analyses will be presented by subject groups as described in items 1 to 5 of Section 5.1 for the SAS. Tables will also be provided for Phase 1 dose escalation by assigned dose groups in the DDS.

Cycle duration is defined as the period from Day 1 of each cycle to one day prior to the Day 1 of the subsequent cycle; for the last cycle, the end date is the date of last dose.

For subjects who discontinued from study treatment but restarted AG-221, the data after restarting AG-221 will not be used for analysis in this section, however, will be presented separately in listings.

9.1. Treatment Duration and Exposure

Duration of treatment (months) is defined as: (treatment end date – treatment start date + 1)/ 30.4. The treatment start date is the date of the first dose of study drug, and the treatment end date is the last dose date. For subjects who are still on treatment at a data cut-off date, treatment end date will be the earlier date of data cut-off date and last day that the subjects take study drug.

Duration of treatment exposure (months) is defined as: (Treatment end date – treatment start date + 28)/30.4. If death date is after treatment end date and earlier than 28 days after treatment end date, duration of treatment exposure is defined as: (Death date – treatment start date + 1)/ 30.4.

Treatment duration and exposure will be summarized by investigator assessed best response for the combined Phase 1, Phase 2, and the combined Phase 1/2 R/R AML subjects and overall.

A subject data listing of study drug records will be provided.

9.2. Cumulative Dose

Cumulative dose is defined as the sum of all doses taken during the treatment period in mg.

9.3. Average Daily Dose

Average daily dose is defined as the cumulative dose divided by number of days dosed. A single average value will be computed for each subject, and then the descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) will be computed for each subject group.

9.4. Dose Intensity

Dose intensity during the treatment is defined as the cumulative dose divided by the treatment duration. The descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) will be computed for each subject group.

Dose intensity for AG-221 = [cumulative dose for AG-221 in mg] / [treatment duration in days].

[redacted]

9.5. Relative Dose Intensity

Relative dose intensity is the actual dose intensity as defined in the previous section divided by the planned dose intensity. The planned dose intensity is based on initially assigned daily dose.

Relative dose intensity for AG-221 will also be categorized into <75%, 75% to <90%, 90% to <120%, and ≥120%. The descriptive statistics and frequency counts will be provided by subject group.

9.6. Dose Modification

Dose modification will be summarized by subject group.

The number and percent of subjects who have at least one dose modification, number of dose modification per subject, and type for dose modification including dose increase, reduction, and interruption will be summarized by subject group.

Details of dose adjustments will be provided in a by subject listing.

[redacted]

10. CLINICAL ACTIVITY ANALYSIS

Efficacy endpoints will be analyzed for the Phase 1 and Phase 2 portions of study separately as well as for the combined Phase 1/2 in R/R AML subjects. All efficacy analyses will be performed in the FAS unless otherwise specified. The primary endpoint will be analyzed in the EAS to provide supportive evidence.

Phase 1:

Efficacy analyses will be primarily presented for Phase 1 dose escalation by total daily dose groups, Part 1 Expansion by cohorts, and the combined Phase 1 by malignancy type and by total daily dose of <100 mg, 100 mg, and >100 mg in R/R AML as described in items 1 to 3 of Section 5.1.

Phase 2:

For Phase 2, all efficacy analyses will be conducted for the R/R AML subjects following item 4 of Section 5.1.

Combined Phase 1/2:

Analyses will be conducted primarily for the R/R AML subjects who have received 100mg total daily dose following item 5 of Section 5.1.

10.1. Multiplicity

Efficacy analyses in this single-arm study are aimed to provide treatment effect estimates. Thus, multiplicity is not of concern for this study.

10.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint of ORR is defined as the rate of responses including CR, CRi, CRp, PR, mCR (for MDS) and MLFS (for AML) by investigator assessment. The ORR will be summarized by the percentage of responses primarily in the FAS with 2-sided exact binomial 95% CI.

Response will also be summarized by the best objective response following the hierarchical order of CR, CRi/CRp, PR, mCR/MLFS, stable disease, relapse/progressive disease/failure, and not evaluable (NE).

An observed ORR in the pivotal Phase 2 R/R AML FAS subjects with the lower bound of the exact binomial 95% CI greater than 25% is deemed clinically meaningful and exceeds the expected ORR with other available therapies. This will be considered as evidence of clinically significant activity of AG-221. The analyses in the combined Phase 1/2 R/R AML on total daily dose of 100mg utilize larger population and thus provide robust estimate of ORR to better describe the clinical activity of AG-221.

To assess the robustness of the primary analysis, the following sensitivity analyses will be performed:

(1) ORR in the EAS for the combined Phase 1, Phase 2, and the combined Phase 1/2;

[redacted]

(2) The ORR assessed by Independent Response Adjudication Committee (IRAC) in the FAS for Phase 1, Phase 2, and the combined Phase 1/2 R/R AML.

10.3. Analyses of Secondary Efficacy Endpoints

The key secondary endpoints include the rates of CR, CR/CRh and CR/CRi/ CRp, DOR, OS, and 56-day independence of RBC and Platelet transfusion. In addition, the following secondary efficacy endpoints are being evaluated as well: EFS, DOCR, DOCR/CRh, TTR, TTBR, TTCR, and TTCR/CRh.

Kaplan-Meier (KM) methods will be utilized to estimate time-to-event endpoints. Counts and percentages will be used to describe categorical variables. Mean (SD), median, and range will be provided to descriptively summarize continuous variables.

10.3.1. Key Secondary Efficacy Endpoints

10.3.1.1. Complete Response Rate

CRR is defined as the rate of CR according to modified IWG response criteria.

Number and percentage of subjects with CR and the 2-sided exact binomial 95% CI for CRR will be summarized for Phase 1 dose escalation, Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2 for the FAS as described in items 1 to 5 of Section 5.1.

The following sensitivity analyses will be performed for Phase 1, Phase 2, and the combined Phase 1/2 :

(1) CRR in the EAS;

(2) CRR assessed by IRAC in the FAS.

10.3.1.2. Rate of CR/CRh

CR/CRh is defined as the rate of subjects with the best response of CR or CRh. Since CRh is not initially defined in the modified IWG criteria and therefore is not available from the investigator assessment. The analyses of CR/CRh will be based on the IRAC assessment.

Number and percentage of subjects with CR/CRh and the 2-sided exact binomial 95% CI will be summarized for Phase 1, Phase 2, and the combined Phase 1/2 in the FAS.

10.3.1.3. Rate of CR/CRi/CRp

This key secondary efficacy endpoint of CR/CRi/CRp is defined as the rate of subjects with the best response of CR, CRi, or CRp. The CR/CRi/CRp rate will be summarized by the percentage of responses primarily in the FAS with 2-sided exact binomial 95% CI for Phase 1 dose escalation, Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2 for the FAS as described in items 1 to 5 of Section 5.1.

The following sensitivity analyses will be performed:

(1) CR/CRi/CRp rate in EAS;

(2) CR/CRi/CRp rate assessed by IRAC in the FAS.

[redacted]

10.3.1.4. Duration of Response

Among subjects who have a response of CR, CRi, CRp, PR, or mCR/MLFS by investigator assessment, DOR will be calculated as the date of the first documented response to the date of the first documented disease relapse, progression or death due to any cause, whichever occurs first. Subjects without relapse, progressive disease, or death due to any cause will be censored at the date of the last adequate response assessment.

Table 3: Censoring Rules for Duration of Response

End Date for Duration of Response	Censored (Y,N)	Scenarios
The earliest of death date, relapse date, and progression date	N	A subject has less than 2 consecutive missing response assessments prior to a documented death, relapse, or progression which is before any subsequent anti-cancer therapy.
The last adequate response assessment date before missing assessments	Y	A subject has 2 or more consecutive missing response assessments prior to a documented death, relapse, or progression.
The last adequate assessment date	Y	If a subject did not die, did not relapse or progression, and did not receive any subsequent anti-cancer therapy.
The last adequate assessment date on or prior to the start of subsequent anti-cancer therapy	Y	If a subject did not die, did not relapse or progression on or prior to subsequent anti-cancer therapy.
The last adequate assessment date on or prior to the start of subsequent AML therapy	Y	If a subject died, relapsed, or had disease progression after receiving subsequent anti-cancer therapy.
1) If response assessment after a single documented progressive disease /relapse shows response including CR, CRi, CRp, PR, mCR/MLFS, the relapse/progression before documented response is considered as NE. 2) Subsequent anti-cancer therapy in this table excludes HSCT.		

DOR will be summarized primarily based on investigator assessment. The DOR will be analyzed using KM methods and KM curves. The 25th percentile, median and 75th percentile of the response duration with 2-sided 95% CI will be provided for overall responders in the FAS for Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2 as described in items 2 to 5 of Section 5.1. KM estimates at 3, 6, 9 and 12 months will be provided at individual time points. Due to the limited sample size of each total daily dose group, DOR will not be analyzed for Phase 1 dose escalation.

The sensitivity analyses for DOR in overall responders regarding censoring rules will be conducted for the combined Phase 1, Phase 2, and the combined Phase 1/2:

- Subjects who undergo HSCT will be censored at the last adequate assessment prior to HSCT;
- Subjects with 2 or more consecutive missing response assessments prior to an event (death, relapse or disease progression) and/or subjects with subsequent anti-cancer therapies prior to an event will be considered as events at the event date by ignoring the missing assessments and subsequent anti-cancer therapies

In addition, a sensitivity analysis for the confirmed progression will be performed to examine the impact of unreliable progressive disease assessment where a single documented relapse or progression immediately followed by a response will be considered as the first relapse/progression.

The DOR will be analyzed based on the IRAC adjudicated response to support the primary results by investigator assessment. Sensitivity analyses regarding censoring rules will be performed for IRAC DOR.

10.3.1.5. Overall Survival

Overall survival is defined as the time from first dose to the date of death due to any cause. Subjects alive will be censored at the last date known to be alive or a pre-specified data cut-off date, whichever is earlier. The last known alive date is the last non-imputed date of any subject record in the study database. This date may be the last visit date or last contact date that the subject is known to be alive. Subjects who only have a baseline record will be censored at the first dose date.

The OS will be primarily analyzed in the FAS for the Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2 as described in items 2 to 5 of Section 5.1. Due to the limited sample size of each total daily dose group, OS will not be analyzed for Phase 1 dose escalation.

The survival distribution of OS will be estimated using the KM methods. The 25th percentile, median and 75th percentile time with two-sided 95% CI will be provided. KM curves will be provided as well. In addition, KM methods will also be used to estimate the survival probabilities at 3, 6, 9 and 12 months.

Sensitivity analyses for OS will be conducted for the combined Phase 1, Phase 2 and the combined Phase 1/2 where transplanted subjects will be censored at HSCT.

10.3.1.6. 56-Day Transfusion Independence Rate

Subjects who achieved post-baseline 56-day RBC transfusion independence i.e. without RBC transfusion for at least 56 consecutive days post baseline during treatment exposure period will be summarized by baseline RBC transfusion dependence status (Yes vs. No). Subjects with at least one transfusion during the baseline period are considered transfusion dependent at baseline. Baseline period is defined as 28 days before and 28 days after the first dose of treatment for Phase 1, and 56 days before the first dose date for Phase 2.

The post-baseline 56-day Platelet transfusion independence will be analyzed similarly. Subjects who achieved both RBC and Platelet 56-day transfusion independence post baseline during treatment exposure period will be summarized by the status of baseline transfusion dependence i.e. receiving at least one RBC and/or Platelet transfusion during baseline period. Transfusion data will be summarized for the combined Phase 1, Phase 2, and the combined Phase 1/2.

10.3.2. Other Secondary Endpoints

The other secondary endpoints include rate of EFS, DOCR, DOCR/CRh, TTR, TTBR, TTCR, and TTCR/CRh.

10.3.2.1. Event-Free Survival

Event-free survival is defined as the interval from the date of the first dose to the date of documented relapse, progression, or death due to any cause, whichever occurs first. Subjects without an EFS event will be censored according to the rules in Table 3. Subjects who only have a baseline record will be censored at date of the first dose.

The analysis methods for EFS are similar to those for DOR. The KM method will be used to estimate the EFS probabilities at 3, 6, 9 and 12 months. The EFS based on IRAC assessment will also be analyzed for Phase 2 R/R AML subjects.

EFS will be analyzed in the FAS for Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2. Due to the limited sample size of each total daily dose group, EFS will not be analyzed for Phase 1 dose escalation.

10.3.2.2. Duration of Complete Response

Among subjects who achieve a CR, DOCR is defined as the time from the date of the first documented CR to the earlier date of documented disease relapse or death due to any cause, using similar censoring as in Table 3.

Kaplan-Meier methods will be used to estimate DOCR in the FAS subjects with CR for Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2. The corresponding KM curves will be provided as well. The DOCR assessed by IRAC will be analyzed to provide supportive evidence.

10.3.2.3. Duration of CR/CRh

Among subjects who achieve a CR/CRh, DOCR/CRh is defined as the time from the date of the first documented CR or CRh to the earlier date of documented disease relapse or death due to any cause, using similar censoring as in Table 3.

Kaplan-Meier methods will be used to estimate DOCR/CRh in the FAS subjects with CR/CRh for the combined Phase 1, Phase 2, and the combined Phase 1/2. The corresponding KM curves will be provided as well. The DOCR/CRh analyses will be based on IRAC assessments.

[redacted]

10.3.2.4. Time to Response

Time to response will be assessed from the date of first dose to the date of first occurrence of response of CR, CRi, CRp, PR, or mCR/MLFS.

Time to response will be summarized using descriptive statistics in subjects who respond in the FAS for Phase 1 dose escalation, Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2. Time to response will also be summarized by cycle. The time to response by IRAC will also be analyzed.

10.3.2.5. Time to Best Response

Time to best response will be assessed from the date of first dose to the date of first occurrence of best response.

Time to best response will be summarized using descriptive statistics in subjects who respond in FAS for Phase 1 dose escalation, Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2. Time to best response will also be summarized by cycle. The time to best response by IRAC will be analyzed.

10.3.2.6. Time to Complete Response

Time to CR will be summarized using descriptive statistics as assessed from the date of first dose to the date of first response (CR) in subjects with documented CR in FAS for Phase 1 dose escalation, Part 1 Expansion, and the combined Phase 1, Phase 2, and the combined Phase 1/2. Time to CR will also be summarized by cycle. The time to complete response by IRAC will be analyzed.

10.3.2.7. Time to CR/CRh

Time to CR/CRh will be summarized using descriptive statistics as assessed from the date of first dose to the date of first response (CR or CRh) in subjects with documented CR/CRh in FAS for the combined Phase 1, Phase 2, and the combined Phase 1/2. Time to CR/CRh will also be summarized by cycle.

10.4. Subgroup Analysis

Appropriate subgroup analyses for ORR and DOR, CRR, CR/CRh rate, CR/CRi/CRp rate, and OS based on the following variables in the combined Phase 1, Phase 2, and the combined Phase 1/2 R/R AML will be provided using the FAS if data are available and/or clinically meaningful. TTR and TTBR will be summarized by best response by investigator assessment, and transfusion independence rate will be summarized by best response by both investigator and IRAC assessments. The ORR, CRR, CR/CRh rate and CR/CRi/CRp rate by subgroups will be presented in forest plots.

1. Age groups (<60, 60 - <70, 70 - <75, ≥75 years)
2. Gender (male vs female)
3. Region (US vs non-US)
4. Race (white vs non-white)

[redacted]

5. Baseline ECOG PS (Grade 0, 1, 2)
6. Number of prior AML therapies (1, 2, >=3)
7. Prior history of MDS (yes vs no)
8. WHO classification of AML (AML with Recurrent Genetic Abnormalities, AML with Myelodysplasia-Related Changes, Therapy related Myeloid Neoplasms, AML not Otherwise Specified)
9. Prior HSCT for AML (yes vs no)
10. IDH2 gene mutation type (R140 vs R172) for ORR and all secondary endpoints
11. Baseline cytogenetic risk status (poor, intermediate, favorable)
12. Best response by Investigator assessment
13. Best response by IRAC
14. Refractory/Relapse status (primary refractory vs relapse; for combined Phase 1/2 only).
15. R/R AML subtypes (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 subjects with favorable-risk status according to National Comprehensive Cancer Network [NCCN] Guidelines [NCCN v1.2015]. Favorable-risk cytogenetics: inv(16), +(16;16), t(8;21), t(15;17); subjects who have failed 2 or more cycles of first line therapy [consisting of an intermediate intensity chemotherapy, hypomethylating agent, or low dose cytarabine]; for combined Phase 1/2 only).

[redacted]

11. SAFETY ANALYSIS

Unless specified otherwise, the safety data will be summarized and presented by subject groups as described in items 1 to 5 of Section 5.1 for the SAS. In the analysis for MTD, DLT will be summarized for subject in the DDS by assigned dose groups for Phase 1 dose escalation.

11.1. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), which are defined as any AEs that begin or worsen on or after the start of study drug through 28 days after the last dose of study drug. All AEs will be coded using MedDRA version 20.0. The severity will be graded based on NCI CTCAE version 4.03.

A treatment-related TEAE is defined as TEAE that is suspected (possibly or probably related) by the Investigator to be related to the study drug. The incidence of TEAEs will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded 1 to 5 according to the NCI CTCAE version 4.03. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the Investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or death (Grade 5). The Grade 3-4 TEAEs will also be summarized by MedDRA SOC and PT. If a subject experiences the same AE more than once with different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple AEs under the same PT (SOC), then the subject will be counted only once for that PT (SOC).

Analysis of TEAEs of special interest will be presented for combined Phase 1, Phase 2 and the combined Phase 1/2 as described in items 3 to 5 of Section 5.1. Some special interested PTs will be grouped and the TEAEs will be summarized by Grouped Terms and be presented for combined Phase 1/2 as described in item 5 of Section 5.1.

The number of subjects with at least one TEAE will be summarized. Analysis for all TEAEs and Grade 3-4 TEAEs by descending frequency of PT will also be summarized. Tabulations of overall summary of TEAEs, all TEAEs by SOC/PT and Grade 3-4 TEAEs will be summarized by cycles for combined Phase 1, Phase 2, and the combined Phase 1/2. All TEAEs and Treatment-related TEAEs leading to study drug discontinuation, reduction or interruption will be summarized separately. Tables summarizing the incidence of TEAEs will be generated for each of the followings:

1. Overall summary of TEAEs.
2. All TEAEs by SOC and PT.
3. Treatment-related TEAEs by SOC and PT.
4. All TEAEs by descending frequency of PT in total column.
5. All TEAEs with Grade 3-4 by SOC and PT.
6. TEAEs by maximum severity.
7. Treatment-related Grade 3-4 TEAEs by SOC and PT.
8. All TEAE with Grade 3-4 by descending frequency of PT in total column.

[redacted]

9. All serious TEAEs by SOC and PT.
10. All serious TEAEs by decreasing frequency of PT in total column.
11. Treatment-related serious TEAEs by SOC and PT.
12. TEAEs leading to study drug permanently discontinued.
13. Treatment-related TEAEs leading to study drug permanently discontinued.
14. TEAEs leading to study drug dose reduced.
15. Treatment-related TEAEs leading to study drug dose reduced.
16. TEAEs leading to study drug dose interrupted.
17. Treatment-related TEAEs leading to study drug dose interrupted.
18. TEAEs leading to death.
19. Treatment-related TEAEs leading to death.

Appropriate safety subgroup analysis will be presented for the combined Phase 1, Phase 2 and combined Phase 1/2 by total daily dose for R/R AML subjects and by malignancy type as described in item 3 and 5 of Section 5.1. All TEAEs by SOC/PT and the overall TEAE summary table for the following subgroups will be provided when the numbers of subjects are sufficient:

- Age (<60, 60 - <75, ≥75 years)
- Sex (Male vs Female)
- Race (White vs Non-white)
- Region (US vs France)
- WHO classification if AML (AML with Recurrent Genetic Abnormalities, AML with Myelodysplasia-Related Changes, Therapy related Myeloid Neoplasms, AML not Otherwise Specified)
- Baseline ECOG (Grade 0, 1, 2)
- Baseline creatinine clearance (<45, 45-<60, ≥60 mL/min)
- Baseline ANC value ($\leq 0.5 \times 10^9$/L, $0.5 < 1 \times 10^9$/L, $\geq 1 \times 10^9$/L)

Summary of all TEAE, Grade 3-4 TEAE, and Grade 3-4 infection, bleeding and all grade febrile neutropenia by the response period and by study period will be summarized in R/R AML for the combined Phase 1, Phase 2, and combined Phase 1/2 to summarize clinical benefit. DLTs will be summarized for Phase 1 dose escalation by assigned dose group in the DDS.

All TEAEs will be listed by subject. Listings for non-treatment-emergent AEs, DLTs, discontinuations due to AE, AEs for re-enrolled subjects, TEAEs leading to death, TEAEs leading to dose reduction, and SAEs will also be provided.

11.2. Adverse Events of Special Interest

Adverse events of special interest will be selected using the standardized MedDRA Query (SMQ) search criteria or relevant grouped PTs for the combined Phase 1, Phase 2, and combined Phase 1/2 in the SAS.

The following TEAEs of special interest will be summarized:

1. QT prolongation:
    a. Broad scope of SMQ Torsade de pointes/QT prolongation.
2. Differentiation syndrome:

    The Differentiation Syndrome Review Committee (DSRC) will review and confirm selected cases. The analyses listed below will be summarized based on the cases generated by the DSRC.

    a. Incidence of the DS syndrome
    b. Time to first onset of DS syndrome
    c. Potential risk factors will be summarized by subjects with and without DS in the combined Phase 1/2. The potential risk factors are:
        - Age (<60, 60 - <75, ≥75 years)
        - Sex (Male vs Female)
        - Baseline ECOG (Grade 0, 1, 2)
        - IDH2 mutation (R172 vs R140)
        - Number of prior anti-cancer regimens (1, 2-5, >5)
        - Hemoglobin (<10, >=10 g/dL)
        - Platelets (<10, >=10 - < 40, >= 40 x10^9/L)
        - WBC (<2, >=2 - < 5, >=5 - < 10, >=10 - < 50, >= 50 x10^9/L)
        - Bone Marrow Blast (<30%, >=30-<50%, >=50-<70%, >=70%)
        - LDH (<=ULN, >ULN-<2 ULN, >=2ULN)
        - Creatinine Clearance (>= 60, >=45 to < 60, >=30 to <45 mL/min)
        - Cytogenetic risk (Intermediate vs Poor)
        - Prior Hydroxyurea use (None, Discontinued Prior to First Dose, Continued After First Dose)
        - Best Response (CR, Non-CR responder, Non-responder)
        - Time to Response (<2 cycles, >=2-<4 cycles, >=4 cycles)
3. Bilirubinemia:
    a. Narrow scope of Biliary system related investigations, signs and symptoms SMQ

[redacted]

b. Summary of Bilirubinemia SMQ by baseline UGT1A1 gene status will be presented in combined phase 1/2 R/R AML and overall subjects

4. Renal Failure:
   a. Broad scope of Acute renal failure SMQ
5. Hepatic TEAE:
   a. Broad or Narrow scope for all Sub-SMQs Drug related hepatic disorders - severe events only
6. Non-infectious Leukocytosis:
   a. Defined as the occurrent of leukocytosis/WBC increase without concurrent infection and infestations or febrile neutropenia (within -/+ 7 days).
   b. Non-infectious leukocytosis will be summarized in combined Phase 1, Phase 2, and combined Phase 1/2.
   c. Potential risk factors will be summarized by subjects with and without non-infectious leukocytosis in combined Phase 1/2. The potential risk factors are:
      - Age (<60, 60 - <75, ≥75 years)
      - Sex (Male vs Female)
      - Baseline ECOG (Grade 0, 1, 2)
      - IDH2 mutation (R172 vs R140)
      - Number of prior anti-cancer regimens (1, 2-5, >5)
      - Hemoglobin (<10, >=10 g/dL)
      - Platelets (<10, >=10 - < 40, >= 40 x10^9/L)
      - WBC (<2, >=2 - < 5, >=5 - < 10, >=10 - < 50, >= 50 x10^9/L)
      - Bone Marrow Blast (<30%, >=30-<50%, >=50-<70%, >=70%)
      - LDH (<=ULN, >ULN-<2 ULN, >=2ULN)
      - Creatinine Clearance (>= 60, >=45 to < 60, >=30 to <45 mL/min)
      - Cytogenetic risk (Intermediate vs Poor)
      - Prior Hydroxyurea use (None, Discontinued Prior to First Dose, Continued After First Dose)
      - Best Response (CR, Non-CR responder, Non-responder)
      - Time to Response (<2 cycles, >=2-<4 cycles, >=4 cycles)

[redacted]

11.3. Death

Cause of death will be summarized in the SAS with the following categories: on-treatment death, post-treatment death, and overall.

1. All deaths within 28 days of the last dose of study drug.
2. All deaths after 28 days of the last dose of study drug.
3. All deaths.

The 30-day and 60-day death rate will be summarized for all deaths. Death analysis will be summarized for the combined Phase 1, Phase 2 and the combined Phase 1/2 as described in items 3 to 5 of Section 5.1.

A death listing will include deaths for all screened subjects during pre-treatment, on-treatment, and post-treatment periods.

11.4. Clinical Laboratory Evaluations

Descriptive statistics will be provided for clinical laboratory data at baseline, post baseline and changes from baseline. Graphical displays of select laboratory parameters over the course of the treatment will also be provided.

Clinical laboratory values will be graded according to NCI CTCAE version 4.03 for applicable tests. Shift tables of laboratory data from baseline to the worst CTC grade during treatment and from baseline to last value on treatment will be presented.

Unless otherwise specified, all laboratory tables in this section will be produced as described in items 1 to 5 in Section 5.1 for the SAS.

A by-subject listing will be presented for each laboratory.

11.4.1. Hematology

For hematologic parameters, the change from baseline will be summarized by study visit.

For specific hematologic parameters (hemoglobin, platelet counts, ANC, WBC, and RBC), separate figures of hematological parameters change from baseline by investigator assessed and IRAC adjudicated best response in Phase 2 will be plotted for R/R AML subjects.

A shift table representing the shift from the baseline grade to the worst grade, separated by worst (high) and worst (low) assessments, will be provided by study visit for Lymphocytes, ANC, WBC counts, platelet counts, and hemoglobin.

A summary table of >=Grade 1 worsening and >=Grade 3 post baseline will be summarized for above hematology parameters in combined Phase 1/2 R/R AML and overall.

In addition, figures for the mean of hemoglobin, platelet counts, ANC and WBC by visit will be provided for the combined Phase 1, Phase 2 and the combined Phase 1/2.

11.4.2. Clinical Serum Chemistry

For serum chemistry parameters, the change from baseline will be summarized by study visit.

[redacted]

A shift table representing the shift from the baseline grade to the worst grade by study visit will be provided for each of these laboratory tests where CTC grades are available. Shift tables in maximum CTCAE grades of worst (high) and worst (low) assessments will be presented separately for each laboratory parameter.

A summary table of >=one Grade worsening and post baseline >=Grade 3 will be summarized for the chemistry parameters where CTC grades are available in combined Phase 1/2 R/R AML and overall. For total bilirubin, >= one Grade worsening and post baseline >=Grade 2 or post baseline >=2ULN will be summarized in overall and by month.

The proportion of subjects with clinically significant post-baseline change in hepatic and renal function will be summarized based on the criteria presented in the table below. The liver related parameters such as ALT, AST, total bilirubin, composite total bilirubin and ALT, and composite total bilirubin and AST will be summarized by UGT1A1 gene mutation status in combined Phase 1/2 R/R AML and overall.

[redacted]

Table 4: Serum Chemistry Changes of Interest

Chemistry Laboratory Test	Parameters for any value and the last value
ALT	ALT ≥× 3ULN (presented as ≥×3- < × 5 ULN, ≥×5- < ×8 ULN and ≥×8ULN)
AST	AST≥×3ULN (presented as ≥×3- < × 5 ULN, ≥5- < ×8 ULN and ≥×8ULN)
Bilirubin Total	Bilirubin Total ≥ × 2ULN Bilirubin Total ≥ × 3ULN
Total Bilirubin and ALT	Composite of Total Bilirubin ≥ ×2ULN and ALT≥ × 3ULN (ALT presented as ≥×3- < × 5 ULN, ≥5 < × 8 ULN and ≥×8 ULN) concurrent and within 1 cycle of Total Bilirubin elevation and at any time after start of treatment
Total Bilirubin and AST	Composite of Total Bilirubin ≥ × 2ULN and AST ≥× 3ULN, (AST presented as ≥3 < × 5 ULN, ≥5 < × 8 ULN and ≥8 ULN) concurrent and within 1 cycle of Total Bilirubin elevation and at any time after start of treatment
Potassium	Hypokalemia < 3.0 mmol/L and >15% decrease from BL Hyperkalemia > 6.0 mmol/L and >15% increase from BL
Potassium and Uric acid	Composite of concurrent hyperkalemia (potassium >ULN and >25% increase from BL) and hyperuricemia (uric acid >ULN and >25% increase from BL)
Phosphorus and Uric acid	Composite of concurrent hyperphosphatemia (phosphorus >ULN and >25% increase from BL) and hyperuricemia (uric acid >ULN and >25% increase from BL)
Calcium and Uric acid	Composite of concurrent hypocalcemia (calcium <ULN and >25% decrease from BL) and hyperuricemia (Uric acid >ULN and >25% increase from BL)
Magnesium	Hypomagnesemia Grade ≥2 and >25% decrease from BL

11.4.3. Fasting Lipid Panel

Fasting lipid panel includes total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. For subjects with available baseline values, mean values and mean changes from baseline will be presented. The proportion of subjects with clinically meaningful post-baseline increases in lipids will be summarized based on the criteria presented in Table 5 for the dose escalation, dose expansion, combined Phase 1.

Table 5: Changes of Interest in Lipids

Laboratory Test	Parameters for Any Value and the Last Value
LDL Cholesterol	>ULN and >10% increase from BL
LDL-C/HDL-C Ratio	>3.5 and >10% increase from BL

[redacted]

11.4.4. Urinalysis

The results will be listed.

11.4.5. Coagulation Analysis

Coagulation includes the following tests: prothrombin time with international normalized ratio (INR) and partial thromboplastin time. Post baseline and changes from baseline will be analyzed descriptively.

11.4.6. Bone Marrow Blast

Post baseline and changes from baseline will be provided for Bone Marrow Myeloblasts (%). In addition, figures for the mean of Bone Marrow Myeloblasts by visit will be provided for the combined Phase 1, Phase 2, and Phase 1/2 R/R AML.

11.5. Vital Sign Measurements

Unless otherwise specified, all vital sign tables in this section will be produced as described in items 1 to 5 in Section 5.1 for the SAS.

Descriptive statistics for vital signs (except height), both observed values and changes from baseline by scheduled visit, will be summarized.

In addition, a shift table will show the number of subjects with high, normal, low values by treatment group and by parameter at each visit. Normal ranges are defined below (anything lower than the low limit is a low value, anything higher than the upper limit is a high value).

1. Temperature 35-38 ºC
2. Systolic blood pressure (SBP) 100-140 mmHg
3. Diastolic blood pressure (DBP) 60-90 mmHg
4. Pulse 60-100 beats per minute (bpm)
5. Respiration 12-20 bpm

A by-subject listing will be presented for each phase of the study.

11.6. Physical Examination

Descriptive statistics for changes in weight from baseline by visit will be summarized in items 1 to 5 in Section 5.1 for the SAS.

Other abnormal physical examination findings will be captured as medical history (screening) and will be summarized as medical history, or will be captured as AEs and will be summarized as AEs.

A by-subject listing will be presented for each phase of the study.

11.7. Electrocardiograms

Electrocardiogram lab data will be summarized as described in items 1 to 5 of Section 5.1.

[redacted]

Electrocardiogram parameters from the central ECG lab include heart rate, PR interval, QRS duration, RR interval, QT, QTc Fridericia value (QTcF) and QTc Bazett value (QTcB). QTcB is not recorded in the CRF page and will be calculated in the following way: QTcB=QT/sqrt (RR).

Central ECG lab-reported values of ECG parameters and change from baseline values will be summarized at each time point.

Electrocardiogram data for each subject will be provided in a data listing for each phase of the study.

In addition, based on the central ECG lab derived data, the proportion of subjects with maximum post-baseline absolute QTcF and QTcB intervals that fall into following categories will be presented:

1. ≤480 ms
2. >480 to ≤500 ms
3. >500 ms

At maximum post-baseline visits, the proportion of subjects who have an increase from baseline in QTcF and QTcB intervals of the following categories will be presented:

1. ≤30 ms
2. >30 to ≤60 ms
3. >60 ms

Maximum post-baseline absolute value categories and the maximum increase from baseline categories of QTcF will be summarized by baseline QTCF intervals where baseline QTcF intervals are:

1. <=450 ms
2. >450 to <470 ms
3. >=470 to <500 ms
4. >=500 ms

11.8. Left Ventricular Ejection Fraction

LVEF data will be summarized for each visit using the SAS as described in items 1 to 5 of Section 5.1. Change from baseline values will be summarized at each visit.

A by-subject listing will be presented for each phase of the study.

11.9. ECOG Performance Status

Shift tables will be provided for ECOG PS from baseline to post baseline by visit, and from baseline to worst/best/last values across all visits. ECOG data will be summarized in SAS as described in items 1 to 5 of Section 5.1.

A by-subject listing will be presented for each phase of the study.

12. INTERIM ANALYSIS

Formal interim analyses based on the cut-off dates of 15 April 2016 and 14 Oct 2016 for the NDA submission in US and the cut-off date of 01 Sep 2017 for the MAA submission in EU have been undertaken to evaluate the clinical efficacy and safety data of the study treatment for Phase 1 and Phase 2 subjects. In addition, periodically interim reviews of the safety data have been conducted by the Clinical Study Team following completion of each dosing cohort prior to the dose escalation and enrollment in next cohort during Phase 1 dose escalation phase, and every 8 weeks during the Part 1 Expansion phase.

13. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

- The cut-off date of 01 Sep 2017 for the MAA submission was added.
- Use 'response' instead of 'remission' for CR, PR, CRR, etc.
- Add secondary endpoints of CR/CRi/CRp rate, CR/CRh rate, DOCR/CRh, and TTCR/CRh.

15. APPENDICES

15.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

1. **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
2. **Log Dates** are dates recorded in eCRF data logs. Specifically, they are the start and end dates for AEs and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 16.2 (eg, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
3. **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
4. **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.

Dates recorded in comment fields will not be imputed or reported in any specific format.

15.1.1. Calculation Using Dates

Calculations using dates (eg, subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

1. Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug (eg, lenalidomide) plus 1 day. The generalized calculation algorithm for relative day is the following:
   - If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
   - Else use STUDY DAY = TARGET DATE – DSTART.

- Note that Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.

2. Age (expressed in days) is calculated: AGE = CONSENT – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
3. Preference is for using calculated age from clinical database. When not available, calculated age from eCRF or IVRS may be used
4. Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
5. Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:
   - WEEKS = DAYS /7
6. Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:
   - MONTHS = DAYS /30.4

15.2. Date Imputation Guideline

Impute Missing AE/CM/Transfusion Start/Stop Dates:

If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by stop date.

(1) Missing day and month-

- If the year is same as the year of first day on study medication, then the day and month of the start date of study medication will be assigned to the missing fields.
- If the year is prior to the year of first day on study medication, then December 31 will assigned to the missing fields.
- If the year is after the year of first day on study medication, then January 1 will be assigned to the missing fields.

(2) Missing day only-

- If the month and year are same as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.
- If the month and year are before the year and month of first day on study medication, then the last day of the month will be assigned to the missing day.

[redacted]

- If the month and year are after the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.

(3) Missing day, month, and year-

- Included as TEAE

Incomplete Stop Date:

If the start date is non-missing and imputed stop date is before the start date then the imputed stop date will be equal to the start date.

(1) Missing day and month-

- If the year of the incomplete stop date is the same as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dose date of study medication, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the last dose date of study medication, then January 1 will be assigned to the missing fields.

(2) Missing day only-

- If the month and year of the incomplete stop date are the same as the month and year of the last dose date of study medication, then the day of the last dose date will be assigned to the missing day.
- If the month and year of the incomplete stop date are before the month and year of the last dose date of the study medication, then the last day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are after the month and year of the last dose date of study medication, then the first day of the month will be assigned to the missing day.

15.3. Independent Response Adjudication Committee

For both Phase 1 and Phase 2 of the study, eligibility, treatment decisions, and response to treatment have been determined by the investigators based on modified IWG response criteria. Response will also be assessed by an Independent Response Adjudication Committee (IRAC) based on the modified IWG criteria and CRh definition.

[redacted]

Table 6: Proposed Modified International Working Group Response Criteria for Acute Myeloid Leukemia

Category	Definition
Complete response (CR)*	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 × 10^9/L (1000/μL); platelet count >100 × 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 × 10^9/L [100,000/μL])
CR with incomplete recovery (CRi)•	All CR criteria except for residual neutropenia (absolute neutrophil count <1.0 × 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 response (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 response 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.

◊ 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 response. 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 response.

¥ 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.

[redacted]

Table 7: 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	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 $>10 \times 10^9$/L.

[redacted]

Table 8: Proposed Modified International Working Group Response Criteria for Altering Natural History of MDS

Category	Response criteria (Response must last at least 4 weeks)
Complete response	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 response	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 response/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality

[redacted]

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 response/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 response; DFS = disease-free survival; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; MDS = myelodysplastic syndromes; PFS = progression-free survival; PR = partial response.

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 (eg, 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.

[redacted]

15.4. Schedules of Assessments

Table 9 and Table 10 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 11 and Table 12 provide the PK and PD sampling and ECG schedule for subjects enrolled in Phase 1 and for subjects enrolled in Phase 2, respectively.

Table 9: Schedule of Assessments: Phase 1 (Dose Escalation and Part 1 Expansion)

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
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 11													
Serial single 12-lead ECG[9]															
ECHO/MUGA for LVEF	X								X[10]			X[10]			
Gene Mutation Analysis[11]	X														
UGT1A1 Gene Testing	X														

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**
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]	
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 11													
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		

[redacted]

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**
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 11 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 (eg, 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. 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. 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 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, 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.

[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).

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

[26] Refer to Table 11 for complete serial PK/PD sampling schedule.

[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.

[redacted]

Table 10: 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 **Error! Reference source not found.**														
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			

[redacted]

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**
Bone Marrow Biopsy and Aspirate[17,18]	X						X			X		X	X		X[13]	
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 12**Error! Reference source not found.**														
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 12 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. 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. 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. 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.
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 12 for complete serial PK/PD sampling schedule.
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.

[redacted]

[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.

[redacted]

Table 11: Pharmacokinetic and Pharmacodynamic Sampling and Electrocardiogram Schedule for 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	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[4]	X[5]	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
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																										

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

Note: For all days with pre-dose 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 .

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 120 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: pre-dose (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.

[redacted]

Table 12: 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	Blood	Triplicate ECG[2]	Blood	Blood	Triplicate ECG[2]	Blood	Blood	Single ECG	Blood	Triplicate ECG[2]	Single ECG
Pre-dose[3]	X	X	X	X	X	X	X	X[4]		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

Note: PK refers to blood sample only. For all days with pre-dose 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.

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Date: Monday, 07 October 2019, 01:49 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName: [redacted]
Title: [redacted]
Date: Monday, 07 October 2019, 02:11 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName: [redacted]
Title: [redacted]
Date: Monday, 07 October 2019, 05:14 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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