Official Title: A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ⩾18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation

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16.1.1. PROTOCOL AND PROTOCOL AMENDMENTS

AG120-C-009 Protocol v1.0 (06 January 2017)

Amendment 1, Version 2.0 (07 February 2017) Global/Summary of Changes

Amendment 2, Version 3.0 (24 March 2017) Global/Summary of Changes

Amendment 3, Version 4.0 (14 April 2017) Global/Summary of Changes

Amendment 4, Version 5.0 (31 October 2017) Global/Summary of Changes

Amendment 4, Version 5.1 (04 December 2017) Japan/Summary of Changes

Amendment 4, Version 5.2 (23 April 2018) Japan/Summary of Changes

Amendment 4, Version 5.3 (11 January 2019) France/Summary of Changes

Amendment 4, Version 5.4 (30 May 2019) Germany/Summary of Changes

Amendment 5, Version 6.0 (09 January 2020) Global/Summary of Changes

Amendment 5, Version 6.1 (09 January 2020) Japan/Summary of Changes

Amendment 6, Version 7.0 (04 March 2020) Global/Summary of Changes

Amendment 6, Version 7.1 (04 March 2020) Japan/Summary of Changes

Amendment 7, Version 8.0 (16 December 2020) Global/Summary of Changes

Amendment 7, Version 8.0 (16 December 2020) Germany/Summary of Changes

Amendment 7, Version 8.1 (16 December 2020) Japan/Summary of Changes

Amendment 7, Version 8.2 (26 May 2021) Germany/Summary of Changes

Amendment 8, Version 9.0 (01 July 2021) Global/Summary of Changes

Amendment 8, Version 9.1 (01 July 2021) Japan/Summary of Changes

Amendment 8, Version 9.2 (01 July 2021) Germany/Summary of Changes

Amendment 9, Version 10.0 (29 September 2021) Global/Summary of Changes

Amendment 9, Version 10.1 (29 September 2021) Japan/Summary of Changes

Amendment 9, Version 10.2 (29 September 2021) Germany/Summary of Changes

Amendment 9, Version 10.3 (03 November 2021) (Republic of South Korea)/ Summary of Changes

CLINICAL STUDY PROTOCOL AG120-C-009

A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ≥18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation

Study Sponsor:	Institut de Recherches Internationales Servier (I.R.I.S.) 50, rue Carnot 92284 Suresnes cedex - France
Medical Director:	[redacted], MD [redacted] Servier Pharmaceuticals LLC
Deputy Head:	[redacted], MD, PhD [redacted] I.R.I.S.
Medical Monitor:	[redacted], MD [redacted] Servier Pharmaceuticals LLC
EudraCT Number:	2016-004907-30
Document Version (Date): Revised:	Original Protocol, Version 1.0 (06 January 2017) Amendment 1, Version 2.0 (07 February 2017) (Global) Amendment 2, Version 3.0 (24 March 2017) (Global) Amendment 3, Version 4.0 (14 April 2017) (Global) Amendment 4, Version 5.0 (31 October 2017) (Global) Amendment 4, Version 5.1 (04 December 2017) (Japan) Amendment 4, Version 5.2 (23 April 2018) (Japan) Amendment 4, Version 5.3 (11 January 2019) (France) Amendment 4, Version 5.4 (30 May 2019) (Germany) Amendment 5, Version 6.0 (09 January 2020) (Global) Amendment 5, Version 6.1 (09 January 2020) (Japan) Amendment 6, Version 7.0 (04 March 2020) (Global) Amendment 6, Version 7.1 (04 March 2020) (Japan) Amendment 7, Version 8.0 (16 December 2020) (Global) Amendment 7, Version 8.1 (16 December 2020) (Japan) Amendment 7, Version 8.2 (26 May 2021) (Germany) Amendment 8, Version 9.0 (01 July 2021) (Global) Amendment 8, Version 9.1 (01 July 2021) (Japan) Amendment 8, Version 9.2 (01 July 2021) (Germany) Amendment 9, Version 10.0 (29 September 2021) (Global) Amendment 9, Version 10.1 (29 September 2021) (Japan) Amendment 9, Version 10.2 (29 September 2021) (Germany)

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

CONFIDENTIAL

Sponsor signatories	
I, the undersigned, have read the foregoing protocol for the study and agree to conduct the study in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. **VICE PRESIDENT, CLINICAL DEVELOPMENT:**	
NAME	[redacted]
DATE	10/7/2021
SIGNATURE	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 10/7/2021 | 4:51:13 PM CEST 4BA4996F882148939477447974 0F226C

Contractual signatories	
I, the undersigned, have read the foregoing protocol for the study and agree to conduct the study in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. **HEAD, LATE STAGE AND LIFE CYCLE MANAGEMENT & DEPUTY HEAD ONCOLOGY & IMMUNO-ONCOLOGY THERAPEUTIC AREA:**	
NAME	[redacted]
DATE	10/5/2021
SIGNATURE	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 10/5/2021 | 6:13:57 PM CEST 2FB926350A1C47C08584D909C7F6E915

Sponsor signatories	
I, the undersigned, have read the foregoing protocol for the study and agree to conduct the study in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. **BIOSTATISTICS PROGRAM HEAD OR DESIGNEE:**	
NAME	[redacted]
DATE	10/5/2021
SIGNATURE	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 10/5/2021 | 5:10:31 PM CEST 09B8A8AA35354BF4881904C4F4879B5D

Contractual signatories	
I, the undersigned, have read the foregoing protocol for the study and agree to conduct the study in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. **INVESTIGATOR**	
NAME	
SITE NUMBER	
DATE	
SIGNATURE	

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Assessment of Amendment 9 (Version 10.0)

This amendment is considered substantial because it changes the Sponsor for the study.

The rationale for the protocol amendment is described in the following section; a detailed summary of the amendment changes is provided in a separate document.

Purpose and Rationale for the Protocol Amendment

The primary purpose for the protocol amendment is to change the Sponsor for the study.

2. SYNOPSIS

Name of Sponsor/Company:

I.R.I.S.

Name of Investigational Product:

AG-120 (International Nonproprietary Name: ivosidenib)

Study Title:

A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ≥18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation

Study Center(s):

Up to 190 study centers in 20 countries will participate in this study.

Phase of Development: 3

Study Objectives:

Primary Objective:

- To compare event-free survival (EFS) between AG-120 + azacitidine and placebo + azacitidine.

Key Secondary Objectives:

- To compare the complete remission (CR) rate between AG-120 + azacitidine and placebo + azacitidine.
- To compare overall survival (OS) between AG-120 + azacitidine and placebo + azacitidine.
- To compare the CR + complete remission with partial hematologic recovery (CRh) rate between AG-120 + azacitidine and placebo + azacitidine; CRh will be derived by the Sponsor.
- To compare the objective response rate (ORR) between AG-120 + azacitidine and placebo + azacitidine.

Additional Secondary Objectives:

- To compare the CR + CR with incomplete hematologic recovery (CRi) (including CR with incomplete platelet recovery [CRp]) rate between AG-120 + azacitidine and placebo + azacitidine.
- To compare duration of CR (DOCR), duration of CR + CRh (DOCRh), duration of response (DOR), and duration of CR + CRi (including CRp) (DOCRi) between AG-120 + azacitidine and placebo + azacitidine.
- To compare time to CR (TTCR), time to CR + CRh (TTCRh), time to first response (TTR), and time to CR + CRi (including CRp) (TTCRi) between AG-120 + azacitidine and placebo + azacitidine.
- To assess the safety and tolerability of treatment with AG-120 + azacitidine compared with placebo + azacitidine.
- To compare transfusion requirements (platelet and red blood cell [RBC]; number of units transfused), infection rates, days spent hospitalized, and other efficacy and safety measures that are potentially indicative of clinical benefit between AG-120 + azacitidine and placebo + azacitidine.
- To assess the impact of treatment on quality of life (QoL) using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L.

- To evaluate the pharmacokinetics (PK) of AG-120 as administered in combination with azacitidine.
- To evaluate the PK/pharmacodynamic (PD) relationship of AG-120 and 2-hydroxyglutarate (2-HG) in blood samples in comparison with placebo.
- To compare rates of CR with IDH1 mutation clearance (MC) between AG-120 + azacitidine and placebo + azacitidine.

[redacted]

Methodology:

Study AG120-C-009 is a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of AG-120 + azacitidine vs placebo + azacitidine in adult subjects with previously untreated isocitrate dehydrogenase 1 mutation-positive (IDH1m) AML who are considered appropriate candidates for non-intensive therapy.

Following provision of signed informed consent, all subjects will undergo Screening procedures within 4 weeks (28 days) prior to randomization to determine eligibility. Gene mutation analysis for confirmation of IDH1m disease from a bone marrow and germ-line mutation analysis from a buccal swab will be conducted for all subjects, and can be conducted prior to the 28-day Screening window. Central laboratory confirmation of IDH1m status is required for study eligibility. With Medical Monitor approval, subjects may be eligible and randomized with local IDH1m testing results; however, bone marrow aspirate for central laboratory testing must have been sent with proof of shipment to the central laboratory prior to randomization. In cases where bone marrow aspirate is not available (ie, dry tap), peripheral blood samples may be used for IDH1m confirmation with Medical Monitor approval. Additional Screening procedures include, but are not limited to: medical and medication history; bone marrow aspirate/biopsy for [redacted] complete physical examination; vital signs; 12-lead electrocardiogram (ECG); Eastern Cooperative Oncology Group (ECOG) performance status (PS); echocardiogram (ECHO) or multi-gated acquisition (MUGA; not permitted for subjects in Germany) scan for left ventricular ejection fraction (LVEF); clinical laboratory assessments (hematology, chemistry, coagulation, and serum pregnancy test); QoL assessments; and [redacted].

Subjects eligible for study treatment based on Screening assessments will be randomized 1:1 to receive oral AG-120 or matched placebo, both administered in combination with subcutaneous (SC) or intravenous (IV) azacitidine. Randomization will be stratified by de novo status (de novo AML and secondary AML) and geographic region (United States and Canada; Western Europe, Israel, and Australia; Japan; and rest of world).

Subjects should be treated for a minimum of 6 cycles of combination therapy unless they experience relapse after achieving a CR, CRi (including CRp), or morphologic leukemia-free state (MLFS); disease progression after having previously attained partial remission (PR) or stable disease; unacceptable toxicity (adverse event [AE]); confirmed pregnancy; withdrawal by subject; protocol violation; death; or End of Study.

Treatment will be administered as follows:

- All subjects will receive azacitidine 75 mg/m^2/day SC or IV for the first 1 week (7 days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle in combination with AG-120 or placebo once

daily (QD) on each day of the 4-week cycle. The same schedule should be used for each subject throughout the duration of treatment, when possible.

- Subjects should continue to receive treatment with AG-120 or placebo + azacitidine until death, disease relapse, disease progression, development of unacceptable toxicity (AE), confirmed pregnancy, withdrawal by subject, protocol violation, or End of Study.
  - Disease progression (defined only for subjects who have not previously attained CR, CRi, CRp, or MLFS) is defined as evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: 1) >50% increase in bone marrow blast count over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline); or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level (> 0.5×10^9/L [500/µL] and/or platelet count to >50 $\times 10^9$/L [50,000/µL] non-transfused); 2) >50% increase in peripheral blasts (white blood cell count × % blasts) to >25,000/µL in the absence of treatment-related differentiation syndrome; or 3) new extramedullary disease.
  - Subjects with a response less than CR at 24 weeks or beyond can continue on treatment if demonstrating treatment benefit, defined as any 1 of the following: 1) Transfusion-independence while on study treatment; 2) ANC >0.5×10^9/L (500/µL); or 3) platelet count >50 $\times 10^9$/L (50,000/µL).

All subjects will have the extent of their disease assessed by bone marrow aspirate (extent of disease may be assessed by biopsy if standard of care or in the event of a dry tap or aspicular [diluted] sample) and peripheral blood samples at Screening (or as part of Pre-screening as long as the disease assessment falls within 28 days prior to randomization); Day 1 (±7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter; End of Treatment (EOT); during EFS follow-up on the same schedule; as clinically indicated; and/or any time that disease progression is suspected. The disease assessment schedule should not be altered due to changes in the start of treatment cycles (eg, in the case of a treatment interruption that resulted in a delay to the start of subsequent cycles).

During treatment, response will be evaluated by the Investigator based on modified International Working Group (IWG) Response Criteria for AML and European LeukemiaNet guidelines to determine subject status and continuation on study treatment. Investigator response assessments will be used for the analysis of all efficacy endpoints, unless otherwise defined.

All subjects will undergo safety assessments throughout the treatment period, to include physical examination, vital signs, ECOG PS, ECG, ECHO or MUGA for LVEF as clinically indicated (method per institutional standard of care, with the same method used for an individual subject throughout the study; sites in Germany may only use ECHO), clinical laboratory assessments (hematology, chemistry, and coagulation), and assessment of AEs, AEs of special interest (AESIs), serious AEs (SAEs), AEs leading to discontinuation or death, and concomitant medication use. Toxicity severity will be graded according to the National Cancer Institute Common Terminology Criteria for AEs version 4.03.

Safety data will be reviewed regularly by an Independent Data Monitoring Committee to ensure the safety of the combination therapy. These reviews will occur after the first 6, 12, 24, and 36 subjects have completed 1 cycle of therapy or discontinued, whichever should occur first. Thereafter, safety reviews will be conducted approximately every 6 months until the study is unblinded for analysis of the primary endpoint.

All subjects are to undergo an EOT assessment within 1 week of their last dose of study treatment (AG-120/placebo + azacitidine). If a subject discontinues study treatment at a regularly scheduled visit, EOT assessments may be performed at that visit. A post-treatment safety assessment is to be scheduled 4 weeks (± 3 days) after the last dose of study treatment.

All subjects who discontinue study treatment without experiencing any 1 of the following: death, disease relapse, treatment failure, or withdrawal of consent, will be followed every Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter for EFS until they experience treatment failure, relapse, death, withdraw from the study, or until the time when 173 EFS events have occurred or as deemed necessary by the independent data monitoring committee (IDMC).

Once the study is unblinded, survival follow up will continue. All subjects who are alive after an EFS event will be contacted every 8 weeks for survival follow-up until death, withdrawal by subject, loss to follow-up, or when the Sponsor ends the study.

Primary Endpoint Results and Subsequent Study Unblinding: Once the primary endpoint of EFS is statistically analyzed, the Sponsor will communicate the topline aggregate results of the study to participating site investigators and via public disclosure. Shortly after public disclosure of the topline aggregate results, the Sponsor will communicate to all sites the treatment assignments of all subjects and will also inform sites which of the 2 following scenarios to pursue following unblinding.

If the benefit-risk profile favors treatment, all ongoing subjects randomized to receive placebo + azacitidine who meet key safety eligibility criteria will be given the opportunity to receive AG-120 + azacitidine following unblinding. Subjects who were already receiving AG-120 + azacitidine may continue to receive treatment on the same assessment schedule. Prior to crossover to AG-120, investigators will evaluate subjects for Inclusion Criteria 5 and 6 and Exclusion Criteria 8, 12, 13, and 17 to determine safety eligibility.

If the benefit-risk profile does not favor treatment, crossover will not be permitted; however, all ongoing patients will be permitted to receive their assigned study treatment at the discretion of the treating investigator.

Estimated Number of Subjects (planned):

A total of approximately 200 subjects with previously untreated IDH1m AML will participate in the study.

Investigational Product, Dosage, and Mode of Administration:

AG-120 (500 mg) or matched placebo will be administered orally QD (approximately every 24 hours) during Weeks 1 to 4 in continuous 4-week (28-day) cycles. Subjects may take AG-120 or placebo tablets with or without food. Subjects should be advised that if AG-120/placebo tablets are taken with food, they should avoid consuming a high-fat meal. All subjects will also be advised to avoid grapefruit and grapefruit products.

Azacitidine will be administered SC or IV at a dose of 75 mg/m^2/day for 1 week every 4 weeks until the end of the study (unless they are discontinued from treatment), starting on Day 1 (± 3 days). In the event that 2 or fewer doses are missed during the 7-day dosing period, dosing should continue so that the subject receives the full 7 days of therapy. If 3 or more doses are missed during the 7-day dosing period, the Investigator should contact the Medical Monitor and a decision on dosing will be made on an individual case basis. A full 7 days of azacitidine are required, but as per institutional practice, a schedule of 5 days of daily dosing, followed by no dose received on the weekend and 2 daily doses given again at the start of the next week, is allowed. The same schedule should be used for each subject throughout the duration of treatment, when possible.

On days when both AG-120/placebo and azacitidine are given, AG-120 or placebo will be given prior to azacitidine.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Subjects must meet all of the following criteria to be eligible for inclusion in the study:

1. Be ≥18 years of age and meet at least 1 of the following criteria defining ineligibility for intensive induction chemotherapy (IC):
   a. ≥ 75 years old
   b. ECOG PS = 2
   c. Severe cardiac disorder (eg, congestive heart failure requiring treatment, LVEF ≤50%, or chronic stable angina)
   d. Severe pulmonary disorder (eg, diffusing capacity of the lungs for carbon monoxide ≤65% or forced expiratory volume in 1 second ≤65%)
   e. Creatinine clearance <45 mL/minute
   f. Bilirubin >1.5 times upper limit of normal (× ULN)
   g. Any other comorbidity that the Investigator judges to be incompatible with intensive IC must be reviewed and approved by the Medical Monitor before study enrollment.
2. Have previously untreated AML, defined according to World Health Organization criteria. Subjects with extramedullary disease alone (ie, no detectable bone marrow and no detectable peripheral blood AML) are not eligible for the study.
3. Have an IDH1 mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution, as determined by central laboratory testing (using an investigational polymerase chain reaction [PCR] assay, Abbott RealTime IDH1) in their bone marrow aspirate (or peripheral blood sample if bone marrow aspirate is not available, with Medical Monitor approval).

   (Note: Local testing for eligibility and randomization is permitted with Medical Monitor approval; however, results must state an IDH1 mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution. Bone marrow aspirate [or peripheral blood sample if bone marrow aspirate is not available, with Medical Monitor approval] for central laboratory testing must have been sent with proof of shipment to the central laboratory prior to randomization.)
4. Have an ECOG PS score of 0 to 2.
5. Have adequate hepatic function, as evidenced by:
   a. Serum total bilirubin ≤2 × ULN, unless considered to be due to Gilbert's disease or underlying leukemia, where it must be <3 × ULN.
   b. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤3.0 × ULN, unless considered to be due to underlying leukemia.
6. Have adequate renal function, as evidenced by serum creatinine ≤2.0 × ULN or creatinine clearance >30 mL/min based on the Cockcroft-Gault glomerular filtration rate.
7. Have agreed to undergo serial blood and bone marrow sampling.
8. Be able to understand and willing to sign an informed consent form.
9. Be willing to complete QoL assessments during study treatment and at the designated time points following treatment discontinuation.
10. If female with reproductive potential, must have a negative serum pregnancy test prior to the start of study therapy. Female subjects with reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who have not been naturally postmenopausal for at least 24 consecutive months.

Females of reproductive potential, as well as fertile men with female partners of reproductive potential, must use 2 effective forms of contraception (including at least 1 barrier form) from the time of giving informed consent throughout the study and for 90 days (both females and males) following the last dose of study drug(s). Effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization. Coadministration of AG-120 may decrease the concentrations of hormonal contraceptives.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from the study:

1. Are candidates for intensive IC for their AML.
2. Have received any prior treatment for AML with the exception of nononcolytic treatments to stabilize disease such as hydroxyurea or leukapheresis.
3. Have received a hypomethylating agent for myelodysplastic syndrome (MDS).
4. Subjects who had previously received treatment for an antecedent hematologic disorder, including investigational agents, may not be randomized until a washout period of at least 5 half-lives of the investigational agent has elapsed since the last dose of that agent.
5. Have received prior treatment with an IDH1 inhibitor.
6. Have a known hypersensitivity to any of the components of AG-120, matched placebo, or azacitidine.
7. Are female and pregnant or breastfeeding.
8. Are taking known strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they can be transferred to other medications within ≥5 half-lives prior to dosing.
9. Exclusion Criterion #9 was removed in Protocol Amendment 5, Version 6.0.
10. Have an active, uncontrolled, systemic fungal, bacterial, or viral infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
11. Have a prior history of malignancy other than MDS or myeloproliferative disorder, unless the subject has been free of the disease for ≥1 year prior to the start of study treatment. However, subjects with the following history/concurrent conditions or similar indolent cancer are allowed to participate in the study:
    a. Basal or squamous cell carcinoma of the skin
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast
    d. Incidental histologic finding of prostate cancer
12. Have had significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association Class (NYHA) Class III or IV congestive heart failure, myocardial infarction, unstable angina, and/or stroke.
13. Have a heart-rate corrected QT interval using Fridericia's method (QTcF) ≥470 msec or any other factor that increases the risk of QT prolongation or arrhythmic events (eg, NYHA Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome). Subjects with prolonged QTcF interval in the setting of bundle branch block may participate in the study.

14. Have a known infection caused by human immunodeficiency virus or active hepatitis B virus (HBV) or hepatitis C virus that cannot be controlled by treatment.
15. Have dysphagia, short-gut syndrome, gastroparesis, or any other condition that limits the ingestion or gastrointestinal absorption of orally administered drugs.
16. Have uncontrolled hypertension (systolic blood pressure [BP] >180 mmHg or diastolic BP >100 mmHg).
17. Have clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid during Screening is only required if there is a clinical suspicion of CNS involvement by leukemia during Screening.
18. Have immediate, life-threatening, severe complications of leukemia, such as uncontrolled bleeding, pneumonia with hypoxia or sepsis, and/or disseminated intravascular coagulation.
19. Have any other medical or psychological condition deemed by the Investigator to be likely to interfere with the subject's ability to give informed consent or participate in the study.
20. Are taking medications that are known to prolong the QT interval unless they can be transferred to other medications within ≥5 half-lives prior to dosing, or unless the medications can be properly monitored during the study. (If equivalent medication is not available, heart rate corrected QT interval [QTc] will be closely monitored.)
21. Subjects with a known medical history of progressive multifocal leukoencephalopathy.

Duration of Treatment and End of Study:

Duration of Treatment

Daily treatment with AG-120 + azacitidine or placebo + azacitidine will begin on the first day of Cycle 1. Subjects should be treated for a minimum of six 4-week (28-day) cycles of combination therapy. With Medical Monitor approval, subjects may continue to receive:

- AG-120 or placebo following discontinuation of azacitidine, provided that they are in CR or CRi (including CRp) and need to discontinue azacitidine due to protocol-specified azacitidine-related toxicity (eg, delayed bone marrow recovery), or
- Azacitidine following discontinuation of AG-120 or placebo, provided that they have not met the definition of relapse or progressive disease.

Subjects should continue to receive study treatment until disease relapse, disease progression, development of an unacceptable toxicity (AE), confirmed pregnancy, withdrawal by subject, protocol violation, death, or End of Study.

Subjects with a response less than CR at 24 weeks or beyond can continue on treatment if demonstrating treatment benefit, defined as any 1 of the following: 1) Transfusion-independence while on study treatment; 2) ANC $>0.5 \times 10^9$/L (500/μL); or 3) platelets $>50 \times 10^9$/L (50,000/μL).

EFS Follow-up

All subjects who discontinue study treatment without experiencing any 1 of the following: death, disease relapse, treatment failure, or withdrawal of consent, will be followed every Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter for EFS until they experience treatment failure, relapse, death, withdraw from the study, or until the time when 173 EFS events have occurred or as deemed necessary by the IDMC.

Survival Follow-up

Once the study is unblinded, survival follow up will continue. All subjects who are alive after an EFS event will be contacted every 8 weeks for survival follow-up until death, withdrawal by subject, loss to follow-up, or when the Sponsor ends the study.

End of Study

At the time of the primary endpoint analysis (approximately 173 EFS events or as deemed necessary by the IDMC), the study will be unblinded. Subjects on treatment at that time may continue receiving study drug. After the primary endpoint analysis, and if the benefit-risk profile favors treatment, subjects randomized to placebo may be offered the choice to receive active AG-120. End of Study is defined as the time at which all subjects have died, discontinued the study, are lost to follow-up, or have withdrawn consent; or when the Sponsor ends the study.

Study Assessments: See Schedule of Assessments in body of protocol.

Criteria for Evaluation:

During treatment, response will be evaluated by the Investigator based on modified IWG Response Criteria for AML and European LeukemiaNet guidelines to determine subject status and continuation on study treatment; CRh will be derived by the Sponsor.

Primary Endpoint:

The primary endpoint of the study is EFS, which is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by Week 24.

Key Secondary Endpoints:

- CR rate (CR defined as bone marrow blasts <5% and no Auer rods, absence of extramedullary disease, ANC $\geq 1.0 \times 10^9$/L [1000/μL], platelet count $\geq 100 \times 10^9$/L [100,000/μL], and independence of RBC transfusions).
- OS, defined as the time from date of randomization to the date of death due to any cause.
- CR + CRh rate (CRh is defined as a CR with partial recovery of peripheral blood counts where ANC is $>0.5 \times 10^9$/L [500/μL], and platelet count is $>50 \times 10^9$/L [50,000/μL]; CRh will be derived by the Sponsor).
- ORR, defined as the rate of CR, CRi (including CRp), PR, and MLFS.

Additional Secondary Endpoints:

- CR + CRi (including CRp) rate (CRi [including CRp] is defined as all CR criteria except for residual neutropenia where ANC is $<1.0 \times 10^9$/L [1000/μL] or thrombocytopenia where platelet count is $<100 \times 10^9$/L [100,000/μL]; without platelet transfusion for at least 1 week prior to disease assessment).
- DOCR, among subjects who achieved CR; DOCRh, among subjects who achieved CR or CRh; DOR, among subjects who achieved CR, CRi (including CRp), PR, and/or MLFS; and DOCRi, among subjects who achieved CR or CRi (including CRp).
- TTCR, among subjects who achieved CR; TTCRh, among subjects who achieved CR or CRh; TTR, among subjects who achieved CR, CRi (including CRp), PR, and/or MLFS; and TTCRi, among subjects who achieved CR or CRi (including CRp).
- Vital signs, and the results of ECOG PS, ECG, and ECHO or MUGA for LVEF as clinically indicated (method per institutional standard of care, with the same method used for an individual subject throughout the study; sites in Germany may only use ECHO).
- Clinical laboratory assessments (hematology, chemistry, and coagulation).
- AEs, AESIs, SAEs, and AEs leading to discontinuation or death.
- Concomitant medication use.

- Transfusion requirements (platelet and RBC; number of units transfused), rates of infection, days spent hospitalized, and other efficacy and safety measures that are potentially indicative of clinical benefit.
- Changes from baseline in QoL assessments (EORTC QLC-C30 and EQ-5D-5L).
- Rates of CR with IDH1 MC.
- AG-120/placebo and azacitidine drug exposure, including dose modifications and dose intensities.
- AG-120 and 2-HG concentrations in circulating plasma.

[redacted]

Statistical Methods:

General Statistical Methods:

Summaries will be produced for subject disposition, demographic and baseline disease characteristics, efficacy, safety, PK, and PD, as appropriate. Categorical data will be summarized by frequency distributions (numbers and percentages of subjects). Continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Time-to-event endpoints will be estimated using the Kaplan-Meier (KM) method. Point estimates and 95% confidence intervals (CIs) will be provided where appropriate, and estimates of the median and other quantiles, as well as individual time points (eg, 3-, 6-, and 12-month rates) will be produced.

Analysis for the Primary Endpoint

Event-free survival is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by Week 24. Subjects who do not achieve CR by Week 24 will be considered to have had an event at Day 1 of randomization. For the remaining CR responders, the event time will be the time of either disease relapse or death, whichever occurs first. Event-free survival will be censored upon initiation of a new anticancer therapy should a new therapy be initiated prior to any EFS event. Sensitivity analyses will be performed to explore the robustness of the primary analysis results and will include an analysis based on the stratified log-rank test following the Intent-to-Treat principle, where the time of relapse or death is determined using the actual date of relapse or death without censoring for missing disease assessments or start of subsequent anticancer therapy.

No interim analyses for efficacy are planned. The analysis for the primary endpoint EFS will be performed at the time when 173 EFS events have occurred or as deemed necessary by the IDMC. Event-free survival will be tested using the log-rank test stratified by the randomization stratification factors (de novo status and geographic region). The basis for a claim of efficacy will be the statistical significance of EFS in favor of the AG-120 + azacitidine arm when the 1-sided $p \leq 0.025$ (observed EFS hazard ratio [HR] ≤ 0.742).

The distribution of EFS will be estimated using the KM method. The KM curves and 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% CIs, will be presented for each treatment arm. The KM estimates at individual time points (eg, 3-, 6-, and 12-month rates) will be presented for each treatment arm. A Cox regression model stratified by randomization stratification factors will also be used to estimate the HR of EFS. However, given that the assumption of proportional hazards is not met based on the EFS definition, the overall HR is less meaningful in this context. As EFS is a composite endpoint, the estimates presented separately by each component are more meaningful: CR rate by 24 weeks and EFS among subjects who achieved CR by 24 weeks. For subjects who achieve CR by 24 weeks, the KM curves of the EFS distribution and 25th, 50th (median), and 75th percentiles (if estimable) along with their 2-sided 95% CIs will be presented for each treatment

arm. A Cox regression model stratified by randomization stratification factors will also be used to estimate the HR of EFS for these subjects.

It is assumed that the CR rate by 24 weeks is 20% and 40% for the placebo + azacitidine arm and the AG-120 + azacitidine arm, respectively. For subjects who achieved CR by 24 weeks, a target HR of 0.76 is assumed for EFS (equivalent to a median EFS among responders of 14.6 months in the placebo + azacitidine arm vs 19.2 months in the AG-120 + azacitidine arm, assuming an exponential distribution). Under these assumptions, a total of 173 EFS events are required to provide 80% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis using a stratified log-rank test. Assuming a recruitment period of approximately 44 months, with an accrual rate of 3 subjects per month during the first 10 months and 5 subjects per month thereafter, along with an assumed 5% overall dropout rate, approximately 200 subjects will be randomized to the 2 treatment arms in a 1:1 ratio. Given the above assumptions, it is estimated that the analysis of the primary endpoint for EFS will occur approximately 52 months after the first subject was randomized.

Key Secondary Endpoint Analyses:

Complete remission rate is defined as the proportion of subjects who achieve a CR. A Cochran Mantel-Haenszel (CMH) test will be used to compare CR rate between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

Overall survival is defined as the time from date of randomization to the date of death due to any cause. Kaplan-Meier curves and KM estimates of OS will be presented for each treatment arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-, 6-, and 12-month rates). The log-rank test stratified by the randomization factors will be used to compare OS between the 2 treatment arms. The HR of OS with a 95% CI comparing the AG-120 + azacitidine arm with the placebo+ azacitidine arm will be estimated from a Cox proportional hazards model stratified by the randomization stratification factors.

The CR + CRh rate is defined as the proportion of subjects who achieved a CR or CRh. CRh is defined as having all CR criteria except that ANC is $>0.5 \times 10^9$/L (500/μL) and platelet count is $>50 \times 10^9$/L (50,000/μL). Because CRh is not part of modified IWG response criteria, it will be derived by Sponsor. A CMH test will be used to compare the CR + CRh rate between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

Objective response rate is defined as the rate of CR, CRi (including CRp), PR, and MLFS. The best response is calculated using the following hierarchy: 1) CR; 2) CRi (including CRp); 3) PR; and 4) MLFS. A summary of best response by treatment arm will be produced. A CMH test will be used to compare ORR between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

Additional Secondary Endpoint Analyses:

A CMH test will be used to compare the CR + CRi (including CRp) rate between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented. Kaplan-Meier methods will be used to estimate DOCR, DOCRh, DOR, and DOCRi; subjects without relapse, disease progression, or death, as appropriate, at the time of analysis will be censored at the last response assessment date. Kaplan-Meier estimates of DOCR, DOCRh, DOR, and DOCRi will be presented by treatment arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-, 6-, and 12-month rates). Time to CR, TTCRh, TTR, and TTCRi will be presented by treatment arm using descriptive statistics.

Transfusion requirements (platelet and RBC; number of units), rates of infection, days spent hospitalized, and other efficacy and safety measures that are potentially indicative of clinical benefit will be summarized by treatment arm using descriptive statistics.

Quality of life, as measured by EORTC QLQ-C30, will be evaluated for subjects with a baseline assessment and at least 1 post-baseline QLQ-C30 assessment that generate a score. For total QLQ-C30, each domain score (eg, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), as well as symptom scales, baseline values, and change from baseline for each time point will be summarized by treatment arm using descriptive statistics. Mixed models will also be applied.

A CMH test will be used to compare the rate of CR with IDH1 MC between AG-120 + azacitidine and placebo + azacitidine. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

Safety Analyses:

Safety will be evaluated by vital signs, the results of ECOG PS, ECG, and ECHO or MUGA for LVEF as clinically indicated (method per institutional standard of care, with the same method used for an individual subject throughout the study; sites in Germany may only use ECHO), clinical laboratory assessments (hematology, chemistry, and coagulation), and assessment of AEs, AESIs, SAEs, AEs leading to discontinuation or death, and concomitant medication use. All safety data will be listed by subject and summarized by treatment arm.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2-HG	2-hydroxyglutarate
α-KG	Alpha-ketoglutarate
β-hCG	Beta-human chorionic gonadotropin
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukemia
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BID	Twice daily
BP	Blood pressure
BSC	Best supportive care
BSA	Body surface area
BUN	Blood urea nitrogen
C1D#	Cycle 1, Day #
CI	Confidence interval
C_{max}	Maximum plasma concentration observed
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic (neutrophil and/or platelet) recovery
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction

Abbreviation	Definition
DLT	Dose-limiting toxicity
DOCR	Duration of complete remission
DOCRh	Duration of complete remission with partial hematologic recovery
DOCRi	Duration of complete remission with incomplete hematologic (neutrophil and/or platelet) recovery, including complete remission with incomplete platelet recovery
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event-free survival
ELN	European LeukemiaNet
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
GBS	Guillain-Barre syndrome
GCP	Good Clinical Practice
HR	Hazard ratio
IB	Investigator's Brochure
IC	Induction chemotherapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IDH, IDH1, IDH2	Isocitrate dehydrogenase, 1, 2
IDH1m	Isocitrate dehydrogenase 1 mutation-positive
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technologies
ITT	Intent-to-Treat
IV	Intravenous(ly)

Abbreviation	Definition
IWG	International Working Group
LDAC	Low-dose cytarabine
LVEF	Left ventricular ejection fraction
MC	Mutation clearance
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PPAS	Per-Protocol Analysis Set
PR	Partial remission
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome(s)
PS	Performance status
QD	Once daily
QTcF	Heart-rate corrected QT interval using Fridericia's method
RBC	Red blood cell
ROW	Rest of world
RP2D	Recommended Phase 2 dose

Abbreviation	Definition
R/R	Relapsed or refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SC	Subcutaneous(ly)
SOP	Standard Operating Procedure
$t_{½}$	Half-life
TLS	Tumor lysis syndrome
TTCR	Time to complete remission
TTCRh	Time to complete remission or complete remission with partial hematologic recovery
TTCRi	Time to complete remission with incomplete hematologic (neutrophil and/or platelet) recovery, including complete remission with incomplete platelet recovery
TTR	Time to first IWG response
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

5. INTRODUCTION

5.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a malignancy of myeloid precursor cells, which undergo rapid proliferation, accumulate in the bone marrow, and severely compromise normal blood cell production. Low blood counts result in increased susceptibility to infections, anemia with fatigue, and thrombocytopenia, leading to increased risk of bleeding. Infections account for the greatest cause of AML deaths, while a small portion of patients succumb to fatal bleeding events. Approximately 19,950 people were diagnosed with AML in 2016 in the United States (US) and 10,430 patients will have died from the disease; the age-adjusted incidence rate of AML is approximately 4 per 100,000 men and women per year (NCI, 2015).

The first study of isocitrate dehydrogenase (IDH) mutations in AML reported the identification of the isocitrate dehydrogenase 1 (IDH1) mutation (R132H) in approximately 8% of the 188 cases analyzed (Mardis et al, 2009). In a small cohort of western patients, the IDH1 mutations (R132H, R132C, and R132G) were observed in 6 (8%) of 78 samples (Ward et al, 2010). Subsequently, within a more homogenous group comprised of adult de novo cytogenetically normal AML patients, mutations in IDH1 were found in 14% of the cases (Marcucci et al, 2010). Considering these data, approximately 2800 people will have been diagnosed with IDH1 mutation-positive (IDH1m) AML in the US in 2016; the age-adjusted incidence rate of IDH1m AML is less than 1 per 100,000 individuals per year (NCI, 2015), making this an extremely rare disease.

According to the Surveillance of Rare Cancers in Europe (RARECARE, 2016) project on subjects diagnosed from 1995 to 2002 and archived in 64 European population-based cancer registries, the overall annual crude incidence of AML was 3.7 per 100,000 (4.0 per 100,000 for males and 3.4 per 100,000 for females) (Visser et al, 2012). Based on the incidence data and the total European Union of 27 member states (EU-27) population (as of 2012 publication date), 42,795 new diagnoses of myeloid malignancies occur in the EU-27 annually, including 18,376 cases of AML (43%). The incidence of AML gradually increased with age with an incidence rate per 100,000 of 0.7 for the age group of 0-14 years, 0.8 for the group 15-24 years, 2.4 for the group 25-64 years, and 13.7 for the oldest age group (65 years or older) (Visser et al, 2012).

Current strategies for AML can be generally divided into intensive and non-intensive treatments. Intensive treatments are usually reserved for fit individuals and comprised of induction and consolidation chemotherapy and may also include allogeneic stem cell transplantation. The goal of intensive therapy is to achieve a long-term cure. In contrast, patients unable to receive intensive treatments may be treated with low-intensity therapies consisting of hypomethylating agents, blood product transfusions, and supportive care including antibiotics. The objective of low-intensity therapy is often palliative. The recommendation to treat a patient with intensive vs non-intensive treatment is individualized and incorporates the patient's age, de novo vs secondary nature of their AML, the presence of comorbidities, and other factors. Whereas intensive induction chemotherapy (IC) represents a standard of care for fit patients, the most appropriate treatment for older, unfit patients remains debatable. Unfit patients, typically including elderly patients with AML have an increased incidence of comorbidities (eg, cardiac and pulmonary dysfunction), poor hematologic reserves, and worse Eastern Cooperative

Oncology Group (ECOG) performance status (PS) due to age alone. Acute myeloid leukemia in this patient group is also more likely to be preceded by a myelodysplastic phase and has a higher incidence of unfavorable cytogenetic profiles than younger patients, known risk factors for poor outcome (Appelbaum et al, 2006; Döhner et al, 2017).

Consequently, when compared to younger adults, older adults who receive IC have a lower chance of remission, a higher chance of induction-related mortality, and shorter survival. Thus, while some older adults are eligible to receive IC, the majority are treated with low-intensity therapies or best supportive care (BSC) alone (Buchner et al, 2009; Klepin, 2015; Sperr et al, 2004). Current treatment options for patients who are not considered candidates for intensive IC due to age, ECOG PS, or other comorbidities, or those who choose not to receive IC, include BSC alone, low-dose cytarabine (LDAC), decitabine, or azacitidine (Burnett et al, 2007; Deschler et al, 2006; Fenaux et al, 2010; Kantarjian et al, 2012). Best supportive care, LDAC, decitabine, and azacitidine have been shown to have a median overall survival (OS) of 2, 5, 8, and 10 months, respectively, in older patients who are not candidates for intensive IC (Burnett et al, 2007; Dombret et al, 2008; Dombret et al, 2015; Kantarjian et al, 2012).

5.2. AG-120

5.2.1. Overview

AG-120 (International Nonproprietary Name: ivosidenib) is a potent inhibitor of the IDH1 mutant protein. AG-120 has been evaluated for its potential to inhibit binding and enzymatic activity in a panel of 80 receptors, ion channels, and enzymes. AG-120 is selective, with no significant off-target activity observed. The compound has been demonstrated to reduce 2-hydroxyglutarate (2-HG) levels by >95%, to reverse growth factor-independent growth in vitro, and to induce differentiation in leukemia cell models.

5.2.2. Summary of Nonclinical Data

Details of the nonclinical development program for AG-120 are provided in the Investigator's Brochure (IB). A summary of the key information is provided below.

5.2.2.1. Pharmacokinetic Drug-Drug Interactions

AG-120 is mainly metabolized by cytochrome P450 (CYP)3A4, with minor contributions from CYP2B6 and CYP2C8. Therefore, co-administration with CYP3A4 strong or moderate inhibitors or strong inducers could have an effect on the PK of AG-120.

AG-120 is an inducer of human CYP3A4 and may also be an inducer of CYP2B6, CYP2C8, and CYP2C9.

AG-120 is a weak direct inhibitor of CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 with half-maximal inhibitory concentration (IC_{50}) values >50 µM and shows little or no evidence of direct inhibition of CYP1A2, CYP2B6, or CYP2C9. AG-120 shows no time- or metabolism-dependent inhibition of any of the CYP enzymes evaluated. The likelihood of inhibition of CYP enzymes by AG-120 is, therefore, extremely low.

AG-120 is a substrate of P-glycoprotein (P-gp), but not breast cancer resistance protein (BCRP). However, coadministration of itraconazole (a strong P-gp inhibitor) had no effect on the

maximum concentration (C_{max}) of AG-120 in human subjects, suggesting the involvement of intestinal P-gp in AG-120 disposition in vivo is likely to be minimal. AG-120 is not a substrate of organic anion transporting polypeptide (OATP)1B1 or OATP1B3 transporters.

AG-120 does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter (OAT)1, and organic cation transporter (OCT)2 at clinically relevant concentrations. AG-120 appears to be a weak inhibitor of OATP1B1 and OATP1B3, with IC_{50} values of 9.56 and 22.8 µM, respectively. AG-120 does not inhibit the OAT1- and OCT2-mediated uptake of the probe substrate (IC_{50} >65 µM) but inhibits OAT3 (IC_{50} ~0.322 µM). A physiologically-based pharmacokinetic (PK) simulation predicted an increase (< 30%) in the area under the concentration × time curve of a sensitive OAT3 substrate, suggesting that the potential for clinically relevant drug interactions due to the inhibition of OAT3 appears to be low.

5.2.3. Summary of Clinical Data

The AG-120 clinical development program was initiated in subjects with hematologic malignancies in March 2014 with a Phase 1 dose escalation and expansion study, AG120-C-001 (Section 5.2.3.1). Based on the results of this Phase 1b/2 study, ivosidenib (TIBSOVO®) was approved by the FDA on 20 July 2018 for patients with relapsed or refractory AML with a susceptible IDH1 mutation.

A Phase 1b/2 study of the combination of AG-120 + azacitidine, AG-221-AML-005, was initiated in March 2016 (Section 5.2.3.2).

Refer to the AG-120 Investigator's Brochure (IB) for further details on all studies being conducted with AG-120.

5.2.3.1. Study AG120-C-001

Study AG120-C-001 is evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of AG-120 in subjects with advanced AML and other hematologic malignancies that harbor an IDH1 mutation. The primary objectives of the study are to assess the safety and tolerability of treatment with AG-120 administered daily in subjects with advanced hematologic malignancies, to determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of AG-120 in this population, and to assess the preliminary clinical activity of AG-120 in subjects with relapsed or refractory (R/R) IDH1m AML. The initial dosing regimen was twice daily (BID); based on the favorable PK profile showing a long elimination half-life ($t_{½}$), BID dosing was discontinued after the first cohort and a once daily (QD) dosing regimen was implemented. This ongoing study is divided into a dose escalation phase and a subsequent expansion phase that will allow for a more robust evaluation of the safety profile and clinical anti-leukemia activity.

As of 01 August 2016, a total of 173 subjects had been administered AG-120 during the dose escalation and expansion phases of Study AG120-C-001 across 6 dosing cohorts; 53 subjects remained on treatment.

Overall, 163 (94%) of the 173 subjects had reported at least 1 adverse event (AE). The most commonly reported AEs (≥ 20% of subjects) across all 173 subjects were diarrhea (31%), fatigue (27%), nausea (25%), pyrexia (21%), leukocytosis (21%), and febrile neutropenia (21%). Overall, 100 (58%) of the 173 subjects had reported at least 1 AE assessed as related to treatment

by the Investigator. The most commonly reported related AEs (≥ 10% of subjects) were diarrhea (14%), nausea (13%), fatigue (12%), and prolonged electrocardiogram (ECG) QT (10%).

Fatal AEs were reported in 29 subjects in Study AG120-C-001. Specific AEs leading to death that were reported in more than 1 subject were: bacteremia/sepsis (6 subjects), multi-organ failure (2 subjects), death (2 subjects), and respiratory failure (2 subjects). Other fatal AEs were reported in 1 subject each.

Serious AEs (SAEs) had been reported in 109 (63%) of the 173 subjects as of the data cutoff. The most commonly reported SAEs (≥ 5% of subjects) were febrile neutropenia (17%), leukocytosis (9%), pneumonia (8%), acute promyelocytic leukemia (APL) differentiation syndrome (7%), and pyrexia (7%). In total, 36 subjects experienced SAEs that were considered related to treatment by the Investigator, including: 11 subjects reporting APL differentiation syndrome; 5 subjects each with prolonged QT interval and leukocytosis; and 2 subjects each with diarrhea, nausea, pancytopenia, rash, retinoic acid syndrome, and pleural effusion. All other related SAEs were reported in 1 subject each.

Preliminary analysis of available PK data as of 01 August 2016 has been performed for Study AG120-C-001. AG-120 was administered orally QD or BID in continuous 4-week (28-day) cycles. A total of 173 subjects were treated with doses of 100 mg BID, 300 mg QD, 400 mg QD, 500 mg QD, 800 mg QD, or 1200 mg QD in the dose escalation phase, and 500 mg QD in the dose expansion phase of the study. Pharmacokinetic evaluations included the assessment of dose proportionality for single and multiple dose plasma exposures of AG-120 (maximum plasma concentration observed [C_{max}], area under the curve from time 0 to 24 hours [$AUC_{0\text{-}24hr}$], and area under the curve from time 0 to 72 hours [$AUC_{0\text{-}72hr}$]), steady-state PK, and accumulation ratio. Following both single and multiple doses, exposures of AG-120 increased less than proportionally to dose from 100 to 1200 mg.

Following multiple doses of AG-120, there was no apparent increase in exposure from 500 to 800 mg QD. Following a single dose, $t_{½}$ ranged from 71 to 152 hours, supporting a QD dose regimen. Following multiple doses of 500 mg QD, steady-state was reached within 15 days, with ~2.2 fold accumulation of AUC and ~1.7-fold accumulation of C_{max}. The observed accumulation ratio at steady-state was less than anticipated based on the long $t_{½}$ after a single dose, likely due to the cytochrome P450 (CYP) 3A induction of its own metabolism. Steady-state pre-dose AG-120 trough levels were maintained above the predicted efficacious exposure level throughout treatment.

After multiple doses, plasma 2-HG levels were substantially reduced (up to 99% inhibition, to levels seen in healthy volunteers), and bone marrow 2-HG concentrations were also substantially reduced (up to 99% reduction), at all dose levels tested. There was a good concordance between 2-HG in plasma and bone marrow. The 500 mg QD dose has shown the largest magnitude of plasma 2-HG inhibition for the majority of subjects. The mean plasma 2-HG inhibition was approximately 87% and 93% for dose escalation and expansion, respectively.

Considering that AG-120 was generally well tolerated in study AG120-C-001, the MTD has not been reached in dose escalation, and the encouraging efficacy data in subjects with advanced hematologic malignancies, including R/R AML, the proposed AG-120 dose of 500 mg QD was selected for expansion. Further, exposures are comparable between 500 mg and 800 mg QD, and approximately 70% of Arm 1^{+} subjects have achieved >90% inhibition of 2-HG at 500 mg QD.

As of 01 August 2016, 100 subjects in the study were evaluated for efficacy in the Arm 1^+ Response Evaluable Set, defined as all Arm 1^+ subjects (R/R AML subjects in Arm 1 of expansion and equivalent R/R AML subjects from dose escalation whose starting dose was 500 mg QD and who met Arm 1 eligibility criteria) who had at least 1 post-baseline response assessment or discontinued earlier. Thirty-seven (37%) of the 100 subjects have had Investigator-assessed objective responses as defined by modified International Working Group (IWG) Response Criteria (Cheson et al, 2003) as defined in the protocol. As of 01 August 2016, in the Arm 1^+ Response Evaluable Set, the objective response rate (ORR) was 37% (95% CI: 27.6%, 47.2%); complete remission (CR) rate was 18% (95% CI: 11.0%, 26.9%), based on Investigator response assessments. The CR + complete remission with partial hematologic recovery (CRh) rate was 24% (95% CI 16.0%, 33.6%). CRh was defined as a CR with partial recovery of peripheral blood counts (< 5% bone marrow blasts, ANC >0.5 × 10^9/L [500/µL], and platelets >50 × 10^9/L [50,000/µL]). Because CRh is not part of modified IWG criteria, it was derived by the Sponsor. These results were consistent with the Primary Efficacy Set (N=82; subjects followed at least 4 months or discontinued earlier), where ORR was 39% (95% CI: 28.4%, 50.4%) and CR rate was 18% (95% CI: 10.6%, 28.4%).

Among all dose escalation subjects who were response evaluable (N=78), 30 (39%) of the 78 subjects have had Investigator-assessed objective responses as defined by IWG Response Criteria as of the data cutoff of 01 August 2016. The ORR for these subjects was 39% (95% CI: 27.7%, 50.2%) and CR rate was 18% (95% CI: 10.2%, 28.3%).

Responses in the study have been durable; subjects have been on treatment for up to 24.2 months (N=173; median treatment duration 3.5 months, range >0 to 24.2 months). Among the 100 Arm 1^+ response evaluable subjects, 82 have been followed for at least 4 months or discontinued earlier, 70 have been followed for at least 6 months, and 56 have been followed for at least 8 months. Median response durations were consistent with the Primary Efficacy Set (N=82; subjects followed at least 4 months or discontinued earlier), where median duration of response (DOR) was 6.5 months (95% CI: 4.6, NE); median duration of CR (DOCR) was 5.6 months (95% CI: 4.6, NE). Median OS for the Arm 1^+ Response Evaluable Set (N=100) was 8.7 months (95% CI: 5.8, 10.4, with 51% censoring) as of the data cutoff.

5.2.3.2. Study AG-221-AML-005

Study AG-221-AML-005 is an ongoing Phase 1b/2, open-label, randomized, multicenter trial in subjects with newly diagnosed AML who are ineligible for intensive IC. The safety and efficacy of AG-120 + azacitidine for subjects with an IDH1 mutation and AG-221 + azacitidine for subjects with an isocitrate dehydrogenase 2 (IDH2) mutation is being evaluated. The study comprises a Phase 1b dose-escalation portion and a Phase 2 randomized portion. The Phase 1b portion of the study is evaluating the RP2D of AG-120 or AG-221 administered in combination with azacitidine.

Safety assessments, including vital signs, ECGs, hematology, serum chemistry, cardiac markers, fasting lipid panel, pregnancy testing (for females of reproductive potential), AEs, concomitant medications and procedures, and transfusion requirements are being evaluated regularly throughout the study.

The initiation of this Phase 3 study (AG120-C-009) was predicated on the demonstrated safety of AG-120 (500 mg QD) administered in combination with azacitidine (75 mg/m^2/day SC for

7 days every 28 days) after 6 subjects enrolled in study AG-221-AML-005 completed at least one 28-day cycle of the dosing regimen, or discontinued earlier. No events meeting the criteria for dose-limiting toxicities (DLTs) were reported within the first 28 days of treatment for the first 6 subjects.

DLTs for AG-120 are as follows:

- Hematologic toxicities: While AG-120 is not associated with myelosuppression, azacitidine has a well-characterized association with cytopenia and other hematologic toxicities. For the Phase 1b portion of this study, hematologic toxicities will not be considered as a DLT for AG-120 and will be mitigated through dose modification of azacitidine in subsequent cycles. The Sponsor will convene a dose review team to review hematology lab data at the completion of each cohort to determine whether any warrant a DLT designation.
- Non-hematologic toxicities: All clinically significant non-hematologic toxicities CTCAE Grade ≥3 that are thought to be causally related will be considered DLTs. (Note: Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition.)

Preliminary results from the 23 subjects in the Phase 1b portion of the study who received AG-120 in combination with azacitidine demonstrated that the dosing regimen is safe and has encouraging clinical activity. As of 19 February 2019, the median treatment duration was 15.1 months (range: 0.3-32.2 months), and 10 (43.5%) subjects were continuing to receive treatment in the study.

Frequently reported AEs (> 20% of subjects) were thrombocytopenia (65.2%); nausea (60.9%); diarrhoea (56.5%); anaemia and constipation (52.2% each); febrile neutropenia and pyrexia (43.5% each); dizziness, fatigue, hypokalemia, insomnia, neutropenia, and vomiting (34.8% each); back pain (30.4%); cough, decreased appetite, and electrocardiogram QT prolonged (26.1% each); and headache, injection site erythema, oedema peripheral, and sepsis (21.7% each). Common serious adverse events (SAEs) (≥ 5% of subjects) were febrile neutropenia (39.1%); IDH differentiation syndrome, pyrexia, and sepsis (13.0% each); and lung infection, pneumonia, and syncope (8.7% each). Serious adverse events of IDH differentiation syndrome were related to AG-120.

The ORR was 78.3% (95% CI: 56.30%, 92.54%), and the CR rate was 60.9% (95% CI: 38.54%, 80.29%). The CR + CRh rate was 69.6% (95% CI: 47.08%, 86.79%). CRh is defined as a CR with partial recovery of peripheral blood counts (< 5% bone marrow blasts, ANC >0.5 × 10^9/L [500/µL], and platelets >50 × 10^9/L [50,000/µL]). Because CRh is not part of modified IWG criteria, it was derived by the Sponsor.

5.3. Azacitidine

The 2017 National Comprehensive Cancer Network (NCCN) Guidelines (V1.2017) recommend use of azacitidine (Vidaza®) in patients who are deemed unfit for IC or for intermediate-intensity therapy and for older patients with previously untreated AML (NCCN, 2017). Azacitidine is an analog of the naturally occurring pyrimidine nucleoside cytidine and is classified as an antimetabolite. Azacitidine is approved by the US Food and Drug Administration for 5 subtypes of myelodysplastic syndrome (MDS). Azacitidine is also approved by the European Commission

for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with: intermediate and high-risk MDS, according to the International Prognostic Scoring System (IPSS); chronic myelomonocytic leukemia with 10% to 29% marrow blasts without myeloproliferative disorder; and AML with 20% to 30% blasts and multi-lineage dysplasia, according to World Health Organization (WHO) classification.

Azacitidine has been extensively studied in MDS and has been shown in a large, randomized Phase 3 trial of higher-risk MDS subjects to provide a survival advantage of 9.4 months over conventional care regimens, thus altering the natural course of MDS. The median OS of azacitidine-treated subjects was 24.5 months compared with 15.0 months for the combined conventional care regimen group, which included BSC, LDAC, and intensive IC (Fenaux and Ades, 2009). In the subset of 113 subjects in this study who had AML by WHO criteria (≥ 20% blasts) from the larger MDS group (mean age 70 years, 24% with unfavorable karyotype, median bone marrow blasts 23%), the median OS was 24.5 months (N=55) in the azacitidine arm compared with 16.0 months (N=58) in the conventional care regimen arm (Fenaux and Ades, 2009).

Azacitidine was initially used as a low-intensity treatment for older adults with AML following reports of clinical activity in several small studies. Silverman et al, using WHO AML criteria for diagnosis, reported a median OS of 19.3 months (N=27) in azacitidine-treated subjects compared with 12.9 months (N=25) in subjects who received best standard of care (Silverman et al, 2006). Additionally, Goldberg et al, reported on 33 subjects who received azacitidine (N=11, median age 74 years) or 7+3 intensive IC (N=22, median age 67 years). The median OS was 13.2 months in azacitidine-treated subjects compared with 9.2 months in intensive IC-treated subjects (Goldberg et al, 2006).

More recently, a multicenter, prospective, randomized Phase 3 study (Study AZA-AML-001) in 488 older subjects (≥ 65 years) with untreated AML with >30% blasts who were not candidates for allogeneic bone marrow or stem cell transplantation reported a clinically meaningful improvement in OS with azacitidine treatment (N=241) over conventional care (N=247; 10.4 vs 6.5 months, respectively; hazard ratio [HR]=0.85; 95% CI, 0.69 to 1.03; p=0.1009) (Dombret et al, 2015). Event-free survival (EFS) was modestly improved with azacitidine, although the improvement was not statistically significant (6.7 vs 4.8 months; HR=0.87; 95% CI, 0.72 to 1.05; p=0.1495). A pre-specified sensitivity analysis censoring subjects who received subsequent AML therapy following study drug discontinuation showed that the median OS with azacitidine versus the conventional care regimen was 12.1 months versus 6.9 months, respectively (HR=0.76; 95% CI, 0.60 to 0.96; p=0.0190). Additionally, a nominally significant increase in OS was observed in azacitidine-treated subjects who did not achieve remission (6.9 vs 4.2 months with conventional care; p=0.0170). Transfusion independence, fewer hospitalizations, and improvement in survival were also observed in subjects who did not achieve a CR (Dombret et al, 2015).

All of the aforementioned studies used the standard azacitidine dose of 75 mg/m^2/day administered SC for 7 days of each 4-week (28-day) cycle. The risk of a drug-drug interaction (DDI) between AG-120 and azacitidine is low and there are no anticipated clinically significant overlapping toxicities between the 2 compounds (see the azacitidine IB or local label for further details regarding the available pharmacology, toxicology, drug metabolism, and clinical experience with azacitidine).

5.4. Study Rationale

5.4.1. Purpose of the Study

Acute myeloid leukemia is an aggressive hematologic malignancy with a poor prognosis. Patients not considered candidates for IC because of age and comorbid conditions, poor ECOG PS, or disease-related adverse prognostic risk factors have an especially poor prognosis, with a median survival of 2 to 10 months; these patients are commonly treated with BSC or low intensity therapies such as LDAC or hypomethylating agents, including azacitidine (Burnett et al, 2007; Burnett et al, 2012; Burnett et al, 2013; Dombret et al, 2008; Dombret et al, 2015; Kantarjian et al, 2010; Kantarjian et al, 2012; Oran and Weisdorf, 2012; Visser et al, 2012). Azacitidine, an analog of the pyrimidine nucleoside cytidine, is a DNA methyltransferase inhibitor that has been shown to be associated with sustained decreases in promoter DNA methylation and altered gene expression at critical regulatory pathways (Tsai et al, 2012). In addition, azacitidine is a cytotoxic agent. Treatment with azacitidine has demonstrated clinical activity in AML and an encouraging median OS of 9 to 10 months in patients not considered to be eligible for IC (Dombret et al, 2015; Fenaux et al, 2010; NCCN, 2017; Pleyer et al, 2014; Pleyer et al, 2013; Thepot et al, 2014).

Mutations of the IDH1 enzyme have been identified in several tumors, including AML (Dang et al, 2010; Dang et al, 2009; Yen et al, 2010). The resulting mutant IDH proteins convert alpha-ketoglutarate (α-KG) to the oncometabolite 2-HG, which has been shown to cause DNA hypermethylation by inhibition of methylcytosine dioxygenase TET2 (Figueroa et al, 2010; Turcan et al, 2012) and histone hypermethylation through competitive inhibition of α-KG-dependent Jumonji-C histone demethylases (Tsukada et al, 2006; Turcan et al, 2012; Yamane et al, 2006), thereby leading to broad epigenetic changes and a block in myeloid differentiation (Chowdhury et al, 2011).

AG-120 is a specific inhibitor of IDH1 mutant protein; nonclinical studies have demonstrated that AG-120 effectively inhibits the activity of IDH mutant proteins leading to the reduction of 2-HG in tumors and the reversal of IDH mutation-induced histone and DNA hypermethylation (Kernytsky et al, 2015). Preliminary clinical data from the ongoing studies (AG120-C-001 and AG-221-AML-005) have shown that AG-120 is safe and results in substantial clinical activity (see Section 5.2.3.1 and Section 5.2.3.2).

These data raise the possibility that the combination of an inhibitor of the IDH1 mutant protein with a DNA methyltransferase inhibitor such as azacitidine may lead to an additive or synergistic antitumor effect. Azacitidine reduces DNA methylation levels non-specifically, as it inhibits DNA methyltransferase activity, while AG-120 indirectly reduces DNA methylation levels by depleting 2-HG and restoring enzyme function to α-KG-dependent enzymes. A synergistic interaction between azacitidine and AG-120 could have a combined impact on DNA methylation, either at the same DNA loci or potentially at different loci. Furthermore, nonclinically, the combination of AG-120 + azacitidine has been shown to enhance the differentiation and apoptosis of a leukemic cell line (TF-1) that harbors an IDH1 R132 mutation (Sponsor data on file).

AG-120 has been well tolerated in studies in patients with AML and solid tumors (AG120-C-001 and AG120-C-002). Drug-related overlapping toxicities are not expected to be clinically significant, nor is an overlapping QT signal likely. Extensive independent safety review by an

independent data monitoring committee (IDMC) will be used to continue to monitor for any unexpected combination risks. Primarily, toxicities observed with both azacitidine- and AG-120-treated subjects include disease-related events (neutropenia, infection, fatigue) and GI toxicity (diarrhea, nausea) (see azacitidine and AG-120 IBs for more detail on toxicities of the individual drugs).

5.4.2. Justification of the Study Design

Induction chemotherapy is the standard treatment for younger, fit patients with AML; however, in unfit populations, in patients who are older in age, and in those who have comorbidities, IC treatment remains a matter of debate (see Section 5.1); hypomethylating agents such as azacitidine are often used to attempt to control AML in these populations, given their increased tolerability. There is a need to combine new agents with azacitidine with the goal of increasing the frequency and duration of responses that will translate into prolonged survival, while minimizing toxicities and treatment-related deaths in this population.

Recurring mutations in IDH1 may be important for AML pathogenesis or disease progression (Mardis et al, 2009). Small molecule inhibition of the mutant IDH1 protein represents a promising targeted therapy for AML. Direct inhibition of the gain-of-function activity of the IDH1 mutated protein is intended to inhibit the production of the oncogenic metabolite 2-HG. AG-120 has been evaluated in both nonclinical and clinical studies and has been shown to effectively inhibit the gain-of-function activity of the mutated protein, leading to up to 100% reduction of 2-HG.

Preliminary clinical data from the ongoing, open-label, single-agent Phase 1 study in subjects with R/R AML (AG120-C-001) have shown that AG-120 is generally well tolerated and triggers the differentiation of leukemic blast cells that ultimately lead to reductions in mean plasma 2-HG concentrations and evidence of substantial clinical activity (see Section 5.2.3.1). The development of effective pharmacologic therapies for patients with IDH1m AML addresses a significant unmet medical need.

This is a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical study to evaluate the efficacy and safety of AG-120 + azacitidine versus placebo + azacitidine in subjects with previously untreated IDH1m AML and who are considered appropriate candidates for non-intensive therapy. Acute myeloid leukemia in this patient group is more likely to be preceded by a myelodysplastic phase and has a higher incidence of unfavorable cytogenetic profiles than AML in younger patients, both known risk factors for poor outcome.

The primary endpoint of the study is EFS. Event-free survival as a primary endpoint in randomized Phase 3 studies in subjects with AML has been proposed as a more exact measure of a drug's efficacy than OS (Estey et al, 2016; Othus et al, 2016). Event-free survival can more accurately describe the contribution of a novel therapy to clinical benefit by removing the potentially confounding effects of post-trial therapies, including rescue therapies, supportive care and, potentially, other IDH1-mutant inhibitors. Event-free survival is defined as the time from randomization until treatment failure, relapse from CR, or death from any cause, whichever occurs first. Treatment failure subjects are defined as failure to achieve CR by Week 24. A response of CR represents both disease control and establishment of hematopoiesis in subjects with AML and is an important predictor of OS (Dombret et al, 2015).

5.4.3. Rationale for the Dose Selected

AG-120 was generally well-tolerated in Study AG120-C-001, the MTD has not been reached in the dose escalation phase of the study, and preliminary efficacy data have been encouraging in subjects with advanced hematologic malignancies, including R/R AML. In light of these observations, the proposed AG-120 dose of 500 mg QD was selected for expansion in that study. The same dose was also selected for the ongoing Phase 1b/2 AG-120 + azacitidine combination study AG-221-AML-005 and for the ongoing Phase 1, 7+3 combination study AG120-221-C-001 and will be used for this Phase 3 study.

Plasma AG-120 exposure increases in a less-than-proportional manner across doses from 100 mg BID to 1200 mg QD, nearing a plateau at 500 mg QD. Sustained and consistent plasma 2-HG inhibition has been observed with plasma 2-HG levels reduced to the normal range of healthy volunteers (up to 100% inhibition) at all doses. The 500 mg QD dose has shown a maximum PD effect based on 2-HG levels for the majority of subjects.

Azacitidine has been studied as both a single agent and in combination in AML. A dosing schedule of 75 mg/m^2/day SC for 7 days of each 4-week (28-day) cycle has proven to be well tolerated and has shown both survival and clinical benefit in subjects with AML. Considering the lack of anticipated clinically significant overlapping toxicities and low DDI risk for azacitidine and AG-120, dosing for the combination will be 75 mg/m^2 SC or intravenous (IV) for 1 week (7 days) in this study. This regimen is also consistent with the regimen used in the combination study, AG-221-AML-005.

5.4.3.1. Potential Pharmacokinetic Interactions between AG-120 and Azacitidine

Azacitidine as a Perpetrator on AG-120 Pharmacokinetics

AG-120 is eliminated in humans mainly by metabolism by CYP3A4, with minor contributions from CYP2B6 and CYP2C8 pathways. AG-120 is a substrate of P-gp; however, coadministration of itraconazole (a strong P-gp inhibitor) had no effect on the maximum concentration of AG-120 in human subjects, suggesting the involvement of intestinal P-gp in AG-120 disposition in vivo is likely to be minimal. In vitro studies indicate that azacitidine does not inhibit CYP2B6-, CYP2C8-, CYP2C9-, CYP2C19-, CYP2D6-, or CYP3A4-mediated activities in human liver microsomes up to a concentration of 100 µM, while weak inhibition (< 30% inhibition) of CYP1A2 and CYP2E1 activities has been observed at 100 µM (Chen et al, 2010). There has been no notable report of CYP induction nor P-gp inhibition mediated by azacitidine. Based on the C_{max} (3 µM) for the azacitidine 75 mg/m^2 regimen, the potential for a clinical DDI due to azacitidine inhibition or induction of hepatic metabolism of AG-120 appears to be low. Nevertheless, a population PK analysis will be utilized to evaluate the effect of azacitidine on the PK of AG-120. In this Phase 3 study, PK samples of AG-120 (AG-120 in the presence of azacitidine or placebo) at protocol-specified pre- and post-dose time points will be collected to assess the effect of azacitidine on the steady-state PK of AG-120.

AG-120 as a Perpetrator on Azacitidine Pharmacokinetics

AG-120 is a weak direct inhibitor of CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5, and shows little or no evidence of direct inhibition of CYP1A2, CYP2B6, or CYP2C9. AG-120 is an inducer of CYP3A4 and may be an inducer of CYP2B6, CYP2C8, and CYP2C9. AG-120 does not inhibit P-gp, OATP1B1, OATP1B3, OAT1, or OCT2 at clinically relevant concentrations.

AG-120 appears to be a weak inhibitor of P-gp, OATP1B1, and OATP1B3, with IC_{50} values of ~ 19.6, 9.56, and 22.8 µM, respectively. AG-120 does not inhibit the OAT1- and OCT2-mediated uptake of the probe substrate (IC_{50} >65 µM), but inhibits OAT3 (IC_{50} approximately 0.322 µM). The ability to assess the impact of AG-120 or another agent on the PK of azacitidine may be hampered by the instability of azacitidine in plasma and variable SC absorption in subjects (Rudek et al, 2005). However, AG-120, as a perpetrator, is unlikely to alter the exposure of azacitidine, for the following reasons:

- CYP enzymes are not involved in the clearance of azacitidine. Intracellular phosphorylation is a pivotal step for azacitidine to become active. Further, azacitidine undergoes non-enzymatic hydrolysis in aqueous solution and deamination mediated by cytidine deaminase, which is widely expressed in human tissues such as liver, intestinal epithelium, and whole blood.
- Azacitidine is rapidly absorbed after SC administration and is cleared rapidly with a mean elimination $t_{½}$ of 41 minutes. Steady-state plasma concentration is reached within the first dose, and there is no exposure accumulation after multiple SC doses (Vidaza, 2015).

5.4.3.2. Potential Pharmacodynamic Interaction Between AG-120 and Azacitidine

Azacitidine is not anticipated to reduce the effect of AG-120 on 2-HG inhibition in leukemic blasts. AG-120 monotherapy at doses ≥200 mg daily have resulted in >90% reduction of plasma and bone marrow 2-HG to levels similar to those observed in healthy subjects. In the ongoing Phase 1b/2 Study AG-221-AML-005, peripheral blood for 2-HG assessments is being collected for exploratory purposes. In summary, the risk of clinical DDI between AG-120 and azacitidine is likely to be low.

6. TRIAL OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

The primary objective of the study is to compare event-free survival (EFS) between AG-120 + azacitidine and placebo + azacitidine.

6.1.2. Secondary Objectives

The key secondary objectives of the study are:

- To compare the complete remission (CR) rate between AG-120 + azacitidine and placebo + azacitidine.
- To compare OS between AG-120 + azacitidine and placebo + azacitidine.
- To compare the CR + CRh rate between AG-120 + azacitidine and placebo + azacitidine; CRh will be derived by the Sponsor.
- To compare the ORR between AG-120 + azacitidine and placebo + azacitidine.

Additional secondary objectives are:

- To compare the CR + CR with incomplete hematologic recovery (CRi) (including CR with incomplete platelet recovery [CRp]) rate between AG-120 + azacitidine and placebo + azacitidine.
- To compare duration of CR (DOCR), duration of CR + CRh (DOCRh), duration of response (DOR), and duration of CR + CRi (including CRp) (DOCRi) between AG-120 + azacitidine and placebo + azacitidine.
- To compare time to CR (TTCR), time to CR + CRh (TTCRh), time to first response (TTR), and time to CR + CRi (including CRp) (TTCRi) between AG-120 + azacitidine and placebo + azacitidine.
- To assess the safety and tolerability of treatment with AG-120 + azacitidine compared with placebo + azacitidine.
- To compare transfusion requirements (platelet and red blood cell [RBC]; number of units transfused), infection rates, days spent hospitalized, and other efficacy and safety measures that are potentially indicative of clinical benefit between AG-120 + azacitidine and placebo + azacitidine.
- To assess the impact of treatment on quality of life (QoL) using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L.
- To evaluate the PK of AG-120 as administered in combination with azacitidine.
- To evaluate the PK/PD relationship of AG-120 and 2-HG in blood samples in comparison with placebo.

- To compare rates of CR with IDH1 mutation clearance (MC) between AG-120 + azacitidine and placebo + azacitidine.

[redacted]

6.2. Endpoints

Investigator response assessments per modified IWG response criteria will be used for all efficacy endpoints, with the exception of CRh, which will be derived by the Sponsor.

6.2.1. Primary Endpoint

The primary endpoint of the study is EFS, which is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by Week 24.

6.2.2. Secondary Endpoints

The key secondary endpoints are:

- CR rate (CR defined as bone marrow blasts <5% and no Auer rods, absence of extramedullary disease, ANC $\geq 1.0 \times 10^9$/L [1000/µL], platelet count $\geq 100 \times 10^9$/L [100,000/µL], and independence of RBC transfusions).
- OS, defined as the time from date of randomization to the date of death due to any cause.
- CR + CRh rate (CRh is defined as a CR with partial recovery of peripheral blood counts where ANC is $>0.5 \times 10^9$/L [500/µL], and platelet count is $>50 \times 10^9$/L [50,000/µL]; CRh will be derived by the Sponsor).
- ORR, defined as the rate of CR, CRi (including CRp), PR, and MLFS.

Additional secondary endpoints are:

- CR + CRi (including CRp) rate (CRi [including CRp] is defined as all CR criteria except for residual neutropenia where ANC is $<1.0 \times 10^9$/L [1000/µL] or thrombocytopenia where platelet count is $<100 \times 10^9$/L [100,000/µL]; without platelet transfusion for at least 1 week prior to disease assessment).
- DOCR, among subjects who achieved CR; DOCRh, among subjects who achieved CR or CRh; DOR, among subjects who achieved CR, CRi (including CRp), PR, and/or MLFS; and DOCRi, among subjects who achieved CR or CRi (including CRp).

- TTCR, among subjects who achieved CR; TTCRh, among subjects who achieved CR or CRh; TTR, among subjects who achieved CR, CRi (including CRp), PR, and/or MLFS; and TTCRi, among subjects who achieved CR or CRi (including CRp).
- Vital signs, and results of ECOG PS, ECG, and echocardiogram (ECHO) or multi-gated acquisition (MUGA) for left ventricular ejection fraction (LVEF) as clinically indicated (method per institutional standard of care, with the same method used for an individual throughout the study; sites in Germany may only use ECHO).
- Clinical laboratory assessments (hematology, chemistry, and coagulation).
- AEs, AEs of special interest (AESIs), SAEs, and AEs leading to discontinuation or death.
- Concomitant medication use.
- Transfusion requirements (platelet and RBC; number of units transfused), rates of infection, days spent hospitalized, and other efficacy and safety measures that are potentially indicative of clinical benefit.
- Changes from baseline in QoL assessments (EORTC QLC-C30 and EQ-5D-5L).
- Rates of CR with IDH1 MC.
- AG-120/placebo and azacitidine drug exposure, including dose modifications and dose intensities.
- AG-120 and 2-HG concentrations in circulating plasma.

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

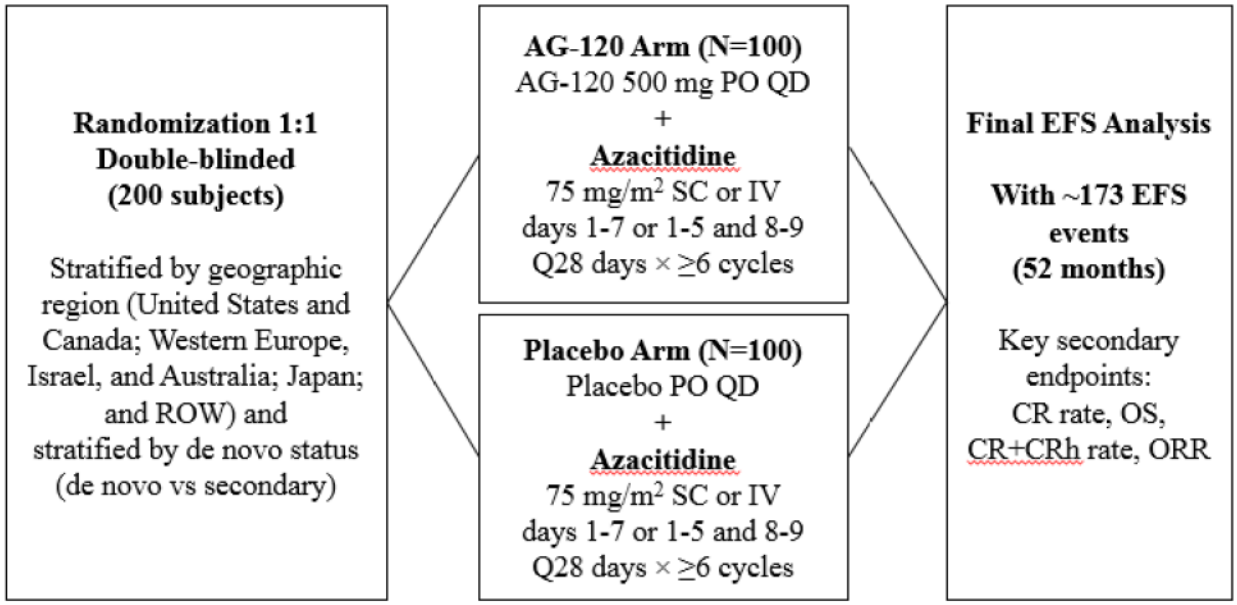
Study AG120-C-009 is a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of AG-120 + azacitidine vs placebo + azacitidine in adult subjects with previously untreated IDH1m AML and who are considered appropriate candidates for non-intensive therapy. Up to 190 study centers in 20 countries will participate in this study.

Following provision of informed consent, all subjects will undergo Screening procedures within 4 weeks (28 days) prior to randomization to determine eligibility. Gene mutation analysis for confirmation of IDH1m disease from a bone marrow and germ-line mutation analysis from a buccal swab will be conducted for all subjects, and can be conducted prior to the 28-day Screening window. Central laboratory confirmation of IDH1m status is required for study eligibility. With Medical Monitor approval, subjects may be eligible and randomized with local IDH1m testing results; however, bone marrow aspirate for central laboratory testing must have been sent with proof of shipment to the central laboratory prior to randomization. In cases where bone marrow aspirate is not available (ie, dry tap), peripheral blood samples may be used for IDH1m confirmation with Medical Monitor approval. Additional Screening procedures include, but are not limited to: medical and medication history; bone marrow aspirate/biopsy for [redacted]; complete physical examination; vital signs; 12-lead ECG; ECOG PS; ECHO or MUGA scan for LVEF (method per institutional standard of care, with the same method used for an individual subject throughout the study; in Germany, only ECHO will be performed); clinical laboratory assessments (hematology, chemistry, coagulation, and serum pregnancy test); QoL assessments; and [redacted].

Subjects eligible for study treatment based on Screening assessments will be randomized 1:1 to receive oral AG-120 or matched placebo, both administered in combination with SC or IV azacitidine. Randomization will be stratified by de novo status (de novo AML and secondary AML) and geographic region (United States and Canada; Western Europe, Israel, and Australia; Japan; and rest of world).

An overview of the study design is provided in Figure 1.

Figure 1: Schema for Study AG120-C-009



Abbreviations: CR = complete remission; CRh = CR with partial hematologic recovery; EFS = event-free survival; IV = intravenous; ORR = objective response rate; OS = overall survival; PO = oral; Q = every; QD = once daily; ROW = Rest of World; SC = subcutaneous.

Subjects should be treated for a minimum of 6 cycles of combination therapy unless they experience relapse after achieving a CR, CRi (including CRp), or MLFS; disease progression prior to achieving CR, CRi (including CRp), or MLFS; unacceptable toxicity (AE); confirmed pregnancy; withdrawal by subject; protocol violation; death; or End of Study.

Treatment will be administered as follows:

- All subjects will receive azacitidine 75 mg/m^2/day SC or IV for the first week (7 days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle in combination with AG-120 or placebo QD on each day of the 4-week cycle. The same schedule should be used for each subject throughout the duration of treatment, when possible.
- Subjects should continue to receive therapy with AG-120 or placebo + azacitidine until death, disease relapse, disease progression, development of unacceptable toxicity (adverse event), confirmed pregnancy, withdrawal by subject, protocol violation, or End of Study (defined in Section 9.11.1).
  - Disease progression (defined only for subjects who have not previously attained CR, CRi, CRp, or MLFS) is defined as evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: 1) >50% increase in bone marrow blast count over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline); or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 500/µL, and/or platelet count to >50,000/µL non-transfused); 2) >50% increase in peripheral blasts (white blood cells [WBCs] × % blasts) to >25,000/µL in the absence of treatment-related differentiation syndrome; or 3) new extramedullary disease.

- Subjects with a response less than CR at 24 weeks or beyond can continue on treatment if demonstrating treatment benefit, defined as any of the following: 1) Transfusion-independence while on study treatment; 2) ANC >500/µL; or 3) platelets >50,000/µL.

All subjects will have the extent of their disease assessed by bone marrow aspirate (extent of disease may be assessed by biopsy if standard of care or in the event of a dry tap or aspicular [diluted] sample) and peripheral blood samples at Screening (or as part of the Pre-screening process, as long as it is within 28 days prior to randomization); and Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53 and every 24 weeks thereafter; at EOT; during EFS follow-up on the same schedule; as clinically indicated; and/or any time that disease progression is suspected. The disease assessment schedule should not be altered due to changes in the start of treatment cycles (eg, in the case of a treatment interruption that resulted in a delay to the start of subsequent cycles).

During treatment, response will be evaluated by the Investigator based on modified IWG Response Criteria for AML (Cheson et al, 2003) and European LeukemiaNet (ELN) guidelines (Döhner et al, 2017) to determine subject status and continuation on study treatment (see Section 10.8.1). Investigator response assessments will be used for the analysis of all efficacy endpoints, unless otherwise defined.

All subjects will undergo safety assessments throughout the treatment period, to include physical examination, vital signs, ECOG PS, ECG, ECHO or MUGA for LVEF as clinically indicated (method per institutional standard of care, with the same method used for an individual subject throughout the study; sites in Germany may only use ECHO), clinical laboratory assessments (hematology, chemistry, coagulation), and assessment of AEs, AESIs, SAEs, AEs leading to discontinuation or death, and concomitant medication use. Toxicity severity will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) version 4.03.

Safety data will be reviewed regularly by an IDMC to ensure the safety of the combination therapy. These reviews will occur after the first 6, 12, 24, and 36 subjects have completed 1 cycle of therapy or discontinued, whichever should occur first. Thereafter, safety reviews will be conducted approximately every 6 months until the study is unblinded for the analysis of the primary endpoint. No interim analyses for efficacy are planned.

All subjects are to undergo an EOT assessment within 1 week of their last dose of study treatment (AG-120/placebo or azacitidine). If a subject discontinues study treatment at a regularly scheduled visit, EOT assessments may be performed at that visit. A post-treatment safety assessment is to be scheduled 4 weeks (± 3 days) after the last dose of study treatment.

All subjects who discontinue study treatment without experiencing any 1 of the following: death, disease relapse, treatment failure, or withdrawal of consent, will be followed every Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter for EFS until they experience treatment failure, relapse, death, withdraw from the study, or until the time when 173 EFS events have occurred or as deemed necessary by the IDMC.

Once the study is unblinded, survival follow up will continue. All subjects who are alive after an EFS event will be contacted every 8 weeks for survival follow-up until death, withdrawal by subject, loss to follow-up, or when the Sponsor ends the study.

7.2. Criteria for Study Closure

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

Circumstances that may warrant premature study closure include, but are not limited to:

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

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

7.3. Temporary Modifications Allowed During Public Health Emergencies

In the event of a coronavirus disease 2019 (COVID-19) public health emergency that affects a geographic area (eg, state, province, country, region, continent) and impedes adherence to protocol-specified procedures, certain modifications (Section 7.3.1) are temporarily allowable to ensure subject safety, maintain compliance with GCP, and minimize risks to study integrity; the protocol must be followed to the fullest extent possible.

These modifications are only allowable 1) when consistent with applicable regulations and guidance and 2) for the duration of the COVID-19 public health emergency. During this period, the need for all implemented modifications will be reassessed and the Sponsor will no longer allow these modifications once the situation resolves.

Documented approval from the Sponsor is required before these modifications can be implemented.

Ivosidenib Assessment: The Sponsor has conducted a risk assessment for concomitant use of a COVID-19 vaccine with ivosidenib with specific consideration for the trial population and determined that the COVID-19 vaccine given to a trial subject is considered a simple concomitant medication with no interaction that requires advice on timing of the vaccine or other aspects that need to be mitigated.

Azacitidine Assessment: There is no known interaction (either biological or pharmacological) between investigational product and available authorized COVID-19 vaccines based on the mechanism of action and metabolism of azacitidine. There is limited data on the efficacy and safety of COVID-19 vaccines in patients with cancers, including hematologic malignancies. The efficacy and safety of vaccination in subjects who are receiving azacitidine are unknown. Currently approved or authorized COVID-19 vaccine given to a trial subject is considered as a simple concomitant medication with no anticipated interaction that requires specific advice on timing of the vaccine or other aspects during the treatment period.

7.3.1. Allowable Temporary Modifications

The following temporary modifications are allowed in the event of a COVID-19 public health emergency and must be reported as protocol deviations; refer to Schedule of Assessments (Table 6) for the timing of assessments.

- Alternative distribution of study drug
  - AG-120 may be shipped to a local healthcare provider or pharmacy or, if necessary, directly to a subject. The quantity to be shipped must be reviewed and approved in advance by the Sponsor (or designee), in agreement with the Investigator.
  - Azacitidine may **not** be shipped directly to a subject. Please refer to Section 9.7.2 (Azacitidine) for instructions on management of azacitidine.
  - Secure, trackable delivery methods (delivery service companies [eg, DHL], couriers, and hand delivery) must be used.
  - Sponsor (or designee) approval is required before each shipment. Shipment will only be permitted if, at minimum, a telemedicine visit has been conducted that incorporates appropriate safety assessments.
- Returning unused study drug, empty study drug packaging, and relevant drug diary pages
  - Return of unused study drug and empty study drug packaging may be delayed until the subject's next visit to the study site. In certain circumstances, the nature of the return process may vary (eg, personal protective equipment may be required).
  - Return of paper drug diaries may be delayed. Site, with Sponsor agreement, should provide instructions to subjects regarding timing and method for returning relevant drug diary pages.
- Telemedicine visits for assessments other than patient-reported outcomes (PROs)
  - Telemedicine visits, preferably via video conference, are permissible for all assessments that can be completed via this mode (eg, medical history, concomitant medications, review of adverse events).
- Use of laboratories and healthcare providers not specified in the clinical trial documentation
  - For assessments that cannot be completed via telemedicine, the use of healthcare providers and laboratories that are not specified in the clinical trial documentation (eg, an imaging facility, clinic, or local practice that is more readily accessible by the subject) is permissible for all assessments that can be completed via this mode (eg, blood collection for laboratory assessments, ECG, physical examinations, imaging).

  - Use of a laboratory or healthcare provider not specified in the clinical trial documentation requires coordination between the subject, the investigator, and the subject's local healthcare provider.
  - The investigator must document their review of the results provided by laboratories and healthcare providers not specified in the clinical trial documentation.
- Home health study support
  - For assessments that cannot be completed via telemedicine, home healthcare provider visits are permissible for all assessments that can be completed via this mode (eg, physical examination, collection of clinical laboratory samples).
  - The Sponsor may facilitate and coordinate these visits with the study site.
  - The Investigator must document their review of the results of home healthcare provider visits.
- Virtual informed reconsent in lieu of in-person informed reconsent
  - Reconsent (ie, consenting to an amended version of the protocol) may be completed virtually and documented in the relevant subject medical records. In these instances, reconsent may be completed virtually where allowed by the applicable regulations, and documented in the relevant subject medical records.

8. STUDY POPULATION

8.1. Number of Subjects

A total of approximately 200 subjects with previously untreated IDH1m AML will participate in this study.

8.2. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for inclusion in the study:

1. Be ≥18 years of age and meet at least 1 of the following criteria defining ineligibility for intensive IC:
   a. ≥ 75 years old
   b. ECOG PS = 2
   c. Severe cardiac disorder (eg, congestive heart failure requiring treatment, LVEF ≤50%, or chronic stable angina)
   d. Severe pulmonary disorder (eg, diffusing capacity of the lungs for carbon monoxide ≤65% or forced expiratory volume in 1 second ≤65%)
   e. Creatinine clearance <45 mL/minute
   f. Bilirubin >1.5 times the upper limit of normal (× ULN)
   g. Any other comorbidity that the Investigator judges to be incompatible with intensive IC must be reviewed and approved by the Medical Monitor before study enrollment.
2. Have previously untreated AML, defined according to WHO criteria. Subjects with extramedullary disease alone (ie, no detectable bone marrow and no detectable peripheral blood AML) are not eligible for the study.
3. Have an IDH1 mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution, as determined by central laboratory testing (using an investigational polymerase chain reaction [PCR] assay, Abbott RealTime IDH1) in their bone marrow aspirate (or peripheral blood sample if bone marrow aspirate is not available, with Medical Monitor approval).

   (Note: Local testing for eligibility and randomization is permitted with Medical Monitor approval; however, results must state an IDH1 mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution. Bone marrow aspirate [or peripheral blood sample if bone marrow aspirate is not available, with Medical Monitor approval] for central laboratory testing must have been sent with proof of shipment to the central laboratory prior to randomization.)
4. Have an ECOG PS score of 0 to 2.
5. Have adequate hepatic function, as evidenced by:
   a. Serum total bilirubin ≤2 × ULN, unless considered to be due to Gilbert's disease or underlying leukemia, where it must be <3 × ULN.
   b. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤3.0 × ULN, unless considered to be due to underlying leukemia.

6. Have adequate renal function, as evidenced by serum creatinine ≤2.0 × ULN or creatinine clearance > 30 mL/min based on the Cockcroft-Gault glomerular filtration rate.
7. Have agreed to undergo serial blood and bone marrow sampling.
8. Be able to understand and willing to sign an informed consent form (ICF).
9. Be willing to complete QoL assessments during study treatment and at the designated time points following treatment discontinuation.
10. If female with reproductive potential, must have a negative serum pregnancy test prior to the start of study therapy. Female subjects with reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who have not been naturally postmenopausal for at least 24 consecutive months. Females of reproductive potential, as well as fertile men with female partners of reproductive potential, must use 2 effective forms of contraception (including at least 1 barrier form) from the time of giving informed consent throughout the study and for 90 days (both females and males) following the last dose of study drug(s). Effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization. Coadministration of AG-120 may decrease the concentrations of hormonal contraceptives (Section 9.13.2).

8.3. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Are candidates for intensive IC for their AML.
2. Have received any prior treatment for AML with the exception of nononcolytic treatments to stabilize disease such as hydroxyurea or leukapheresis.
3. Have received a hypomethylating agent for myelodysplastic syndrome (MDS).
4. Subjects who had previously received treatment for an antecedent hematologic disorder, including investigational agents, may not be randomized until a washout period of at least 5 half-lives of the investigational agent has elapsed since the last dose of that agent.
5. Have received prior treatment with an IDH1 inhibitor.
6. Have a known hypersensitivity to any of the components of AG-120, matched placebo, or azacitidine.
7. Are female and pregnant or breastfeeding.
8. Are taking known strong CYP3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they can be transferred to other medications within ≥5 half-lives prior to dosing (Appendix 15.6).
9. Exclusion Criterion #9 was removed in Protocol Amendment 5, Version 6.0.
10. Have an active, uncontrolled, systemic fungal, bacterial, or viral infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.

11. Have a prior history of malignancy other than MDS or myeloproliferative disorder, unless the subject has been free of the disease for ≥1 year prior to the start of study treatment. However, subjects with the following history/concurrent conditions or similar indolent cancer are allowed to participate in the study:
    a. Basal or squamous cell carcinoma of the skin
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast
    d. Incidental histologic finding of prostate cancer
12. Have had significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association Class (NYHA) Class III or IV congestive heart failure (see Appendix 15.2), myocardial infarction, unstable angina, and/or stroke.
13. Have a heart-rate corrected QT interval using Fridericia's method (QTcF) ≥470 msec or any other factor that increases the risk of QT prolongation or arrhythmic events (eg, NYHA Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome). Subjects with prolonged QTcF interval in the setting of bundle branch block may participate in the study.
14. Have a known infection caused by human immunodeficiency virus (HIV) or active hepatitis B virus (HBV) or hepatitis C virus that cannot be controlled by treatment.
15. Have dysphagia, short-gut syndrome, gastroparesis, or any other condition that limits the ingestion or gastrointestinal absorption of orally administered drugs.
16. Have uncontrolled hypertension (systolic blood pressure [BP] >180 mmHg or diastolic BP >100 mmHg).
17. Have clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid during Screening is only required if there is a clinical suspicion of CNS involvement by leukemia during Screening.
18. Have immediate, life-threatening, severe complications of leukemia, such as uncontrolled bleeding, pneumonia with hypoxia or sepsis, and/or disseminated intravascular coagulation.
19. Have any other medical or psychological condition deemed by the Investigator to be likely to interfere with the subject's ability to give informed consent or participate in the study.
20. Are taking medications that are known to prolong the QT interval (Appendix 15.5) unless they can be transferred to other medications within ≥5 half-lives prior to dosing, or unless the medications can be properly monitored during the study. (If equivalent medication is not available, heart rate corrected QT interval [QTc] will be closely monitored as defined in Section 9.13.2).
21. Subjects with a known medical history of progressive multifocal leukoencephalopathy (PML).

8.4. Subject Identification and Registration

Subjects who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria (see Sections 8.2 and 8.3, respectively) have been satisfied and that the subject is eligible for participation in this clinical study. The Medical Monitor will confirm eligibility for all subjects prior to receipt of the first dose of AG-120 or placebo.

8.5. Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time for any reason. A subject's withdrawal from treatment or the study will not jeopardize the relationship with their healthcare providers or affect their future care. Subjects may choose to withdraw from the study treatment but agree to remain on study for follow-up contact. This decision must be recorded in writing by the study site.

Should a subject decide to withdraw, all efforts will be made to complete and report the protocol-defined study observations as completely as possible and to determine the reason for withdrawal.

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

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

8.5.1. Withdrawal from Study Treatment

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

- Withdrawal by subject
- AE
- Death
- Relapse/disease progression
- Treatment failure (subjects with a response less than CR after receiving treatment for at least 24 weeks)
- Clinical progression (within 24 weeks) not confirmed by IWG assessment
- Subject lost to follow-up
- Confirmed pregnancy for female subjects only (study therapy should be immediately interrupted based upon a positive urinary human chorionic gonadotropin [hCG] test, and permanently discontinued if confirmed by a serum beta-human chorionic gonadotropin [β-hCG] test)
- Protocol violation: non-adherence to study treatment regimen or protocol requirements

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the subject is lost to follow-up, or the subject withdraws consent. If a subject withdrew from treatment because of an AE, every effort must be made to perform protocol-specified safety follow-up procedures (see Section 10.6).

8.5.2. Event-Free Survival Follow-up

All subjects who discontinue study treatment without experiencing any 1 of the following: death, disease relapse, treatment failure, or withdrawal of consent, will be followed every Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter for EFS until they experience treatment failure, relapse, death, withdraw from the study, or until the time when 173 EFS events have occurred or as deemed necessary by the IDMC.

8.5.3. Survival Follow-up

Once the study is unblinded, survival follow up will continue. All subjects who are alive after an EFS event will be contacted every 8 weeks for survival follow-up until death, withdrawal by subject, loss to follow-up, or when the Sponsor ends the study.

8.5.4. Withdrawal from the Study

Subjects discontinuing study treatment prior to experiencing disease progression/relapse will continue to be followed for disease progression/relapse/death. The reasons for withdrawal from the study include:

- Withdrawal by subject
- Subject lost to follow-up
- Study terminated by Sponsor
- Death

9. STUDY TREATMENT

9.1. Description of Study Drug

AG-120 will be supplied as 250 mg-strength tablets to be administered orally. Placebo will be supplied as matched tablets to be administered orally. Inactive ingredients of AG-120 tablets are hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, and Opadry® II Blue. The inactive ingredients of placebo to match AG-120 tablets are microcrystalline cellulose, mannitol, magnesium stearate, and Opadry® II Blue.

Azacitidine will be supplied by the Sponsor as a sterile lyophilized powder containing 100 mg azacitidine and 100 mg mannitol per vial, to be reconstituted and administered SC or IV.

AG-120 is provided for investigational use only (considered an investigational medicinal product; IMP) and is to be used only within the context of this study. Azacitidine is also considered an IMP for this Phase 3 study, with the exception of sites in Brazil, where azacitidine will be supplied as commercial product. All study drug products will be supplied by the Sponsor. Please see the respective IBs for further details regarding AG-120 and azacitidine.

9.2. Study Drug Packaging and Labeling

AG-120 and matched placebo will be supplied in appropriate containers with child-resistant closures and will be labeled appropriately as IMP for this study.

Azacitidine will be supplied in sterile single-use vials and will be labeled appropriately as IMP for this study (or for investigational use, for sites in Brazil).

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

9.3. Study Drug Storage

AG-120 tablets, matched placebo tablets, and azacitidine vials must be stored according to the respective package label.

All study drug products must be stored in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator.

9.4. Method of Assigning Subjects to Treatment

Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 ratio to receive AG-120 500 mg orally QD plus 75 mg/m^2/day SC or IV azacitidine or AG-120-matched placebo orally QD plus 75 mg/m^2/day SC or IV azacitidine. Randomization will be stratified by de novo status (de novo AML and secondary AML) and geographic region (United States and Canada; Western Europe, Israel, and Australia; Japan; and rest of world).

The randomization schedule will be generated by an independent statistical group; all study site personnel (Investigators, study coordinators, study pharmacists) and the Sponsor will be blinded to study treatment. The randomization assignment will be implemented by interactive response technologies (IRT).

9.5. Blinding

The subjects, Investigators, Sponsor, and the clinical research unit staff who deal directly with subjects will all be blinded to study treatment assignment. The IRT will assign each subject specific Medication ID-labeled study drug containers and azacitidine vials. AG-120 and matched placebo will be packaged and labeled identically so that the study pharmacist will remain blinded to treatment assignment.

The subjects, Investigators, Sponsor, and the clinical research unit staff will remain blinded for the duration of the study until the final analysis for the primary endpoint unless emergency unblinding is required (see Section 9.6). An IDMC will review unblinded safety data and other clinical data, including efficacy data, at scheduled meetings; the unblinded summaries will be prepared by an independent statistical center (see Section 10.6.1).

9.6. Unblinding

The need to unblind study treatment should first be discussed with the Sponsor's Medical Monitor (or Medical Director). In the event of a medical emergency or pregnancy in a female subject, or in the female sexual partner of a male subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating Investigator. Investigators are encouraged to discuss a plan to break the blinding code with the Medical Monitor.

In the case of an emergency, the Investigator may access the IRT to reveal the identity of the treatment for that subject. Once the decision to unblind has been made, the Investigator must record the nature of the emergency that required the unblinding, along with the date and time of the unblinding on the proper source documentation and notify the Sponsor's Medical Monitor (or Medical Director) of the unblinding.

In the event that a subject's treatment assignment is unblinded, either accidentally or in the case of emergency unblinding, the subject will be allowed to continue study treatment (if there is no disease progression).

In cases where Investigators may need to know prior study treatment assignment, (eg, an SAE is treated differently based on exposure status), an Investigator may request subject unblinding. In such situations and with Medical Monitor approval, the subject and site staff will be unblinded to a subject's treatment assignment after documented disease progression (as assessed by the Investigator and after discussion with the Sponsor's Medical Monitor).

Primary Endpoint Results and Subsequent Study Unblinding: Once the primary endpoint of EFS is statistically analyzed, the Sponsor will communicate the topline aggregate results of the study to participating site investigators and via public disclosure. Shortly after public disclosure of the topline aggregate results, the Sponsor will communicate to all sites the treatment assignments of all subjects and will also inform sites which of the 2 following scenarios to pursue following unblinding.

If the benefit-risk profile favors treatment, all ongoing subjects randomized to receive placebo + azacitidine who meet key safety eligibility criteria will be given the opportunity to receive AG-120 + azacitidine following unblinding. Subjects who were already receiving AG-120 + azacitidine may continue to receive treatment on the same assessment schedule. Prior to

crossover to AG-120, investigators will evaluate subjects for Inclusion Criteria 5 and 6 and Exclusion Criteria 8, 12, 13, and 17 to determine safety eligibility.

If the benefit-risk profile does not favor treatment, crossover will not be permitted; however, all ongoing patients will be permitted to receive their assigned study treatment at the discretion of the treating investigator.

9.7. Study Drug Preparation and Administration

Subjects may not receive study treatment for each treatment cycle until all Day 1 procedures have been completed and all doses of study treatment from the prior treatment cycle have been accounted for, including the number of missed doses (where applicable). For females of reproductive potential, a serum β-hCG pregnancy test (sensitivity of at least 25 mIU/mL) must be performed at Screening within 72 hours prior to study treatment administration and be verified as negative.

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

Subjects will be monitored for hematologic toxicity and non-hematologic (if thought to be causally related) toxicity, with the NCI CTCAE version 4.03 used as a guide for the grading of severity (see Section 11.2). Dosing interruptions or delays or dose modifications may occur for managing toxicities and/or treatment response during study treatment (see Section 9.8).

9.7.1. AG-120 and Matched Placebo

AG-120 (500 mg) or matched placebo will be administered orally QD (approximately every 24 hours) during Weeks 1 to 4 in continuous 4-week (28-day) cycles. Crossover between treatment arms will not be permitted until the study is unblinded and the primary endpoint reaches statistical significance (see Section 9.6). Subjects should be instructed to take their QD dose at approximately the same time each day. Each dose should be taken with a glass of water and consumed over as short a time as possible.

Subjects should be instructed to swallow tablets whole and not to chew the tablets. Subjects may take AG-120 or placebo tablets with or without food. Subjects should be advised that if AG-120/placebo tablets are taken with food, the subject should avoid grapefruit or grapefruit products and avoid consuming a high-fat meal (refer to representative examples of low-fat and high-fat, high-calorie meals in Appendix 15.1).

If the subject forgets to take the daily dose, they should take AG-120 or placebo within 12 hours after the missed dose. If more than 12 hours have elapsed or if the dose was vomited, that dose should be omitted and the subject should resume treatment with the next scheduled dose.

Subjects will be dispensed the appropriate number of Sponsor-packaged, labeled bottles to allow for dosing for a full cycle; alternatively, they may be dispensed appropriate bottle(s) until the next scheduled visit. Subjects are to return all unused tablets (or the empty bottles) on Day 1 (± 3 days) of each treatment cycle or at the next scheduled visit.

Subjects will be given a dosing diary for each treatment cycle. They should record relevant information regarding their study drug in the diary (eg, confirmation that each daily dose was taken, reasons for missed doses).

Treatment compliance (see Section 9.11.3) will be assessed based on the return of unused drug and the dosing diary (see Section 9.12 and Section 9.13).

9.7.2. Azacitidine

Subcutaneous or IV azacitidine will be prepared and administered as detailed in Appendix 15.3.

Subjects will receive azacitidine 75 mg/m^2/day SC or IV for 1 week every 4 weeks until the end of the study, unless they are discontinued from the treatment. A full 7 days of azacitidine is required, but as per institutional practice, a schedule of 5 days of daily dosing, followed by no dose received on the weekend, and 2 daily doses given again at the start of the next week, is allowed. The same schedule should be used for each subject throughout the duration of treatment, when possible.

In the event that 2 or fewer doses are missed during the 7-day dosing period, dosing should continue so that the subject receives the full 7 days of therapy. If 3 or more days are missed during the 7-day dosing period, the Investigator should contact the Medical Monitor, and a decision on dosing will be made on an individual case basis.

On days when both AG-120 or placebo and azacitidine are given, AG-120 or placebo will be given prior to azacitidine.

9.8. Criteria for Dose Escalation, Dose Modification, or Discontinuation of Study Drug

9.8.1. AG-120/Placebo Dose Modification and Stopping Criteria

Intra-subject dose escalation will not be permitted.

For any AE, including AEs not specifically mentioned in Table 1, the Investigator may decide to delay dosing or modify the dose of AG-120/placebo based on clinical judgment. All dose modifications of AG-120/placebo should be discussed with the Sponsor prior to implementation. Dose modifications of AG-120/placebo from 500 mg to 250 mg will be permitted on study for management of AEs (see Table 1). If more than 1 AE occurs that would require a dose modification, upon resolution of all AEs to baseline or Grade 1, AG-120/placebo should be dose-reduced to 250 mg. Subjects who have had their dose of AG-120/placebo reduced due to a Grade ≥3 AE will be permitted to re-escalate to 500 mg after discussion with the Sponsor's Medical Monitor.

Dose delays for reasons other than management of AEs are discouraged. Dose delays up to 28 days will be permitted at the discretion of the Investigator in consultation with the Medical Monitor for reasons including management of AEs and for mitigating circumstances (eg, planned procedures).

Azacitidine and AG120/placebo can be interrupted concurrently, or either agent alone, depending on the attribution to an AE by the Investigator. If azacitidine is permanently discontinued, treatment with AG-120/placebo may continue at the discretion of the Investigator and with the agreement of the Medical Monitor, provided that the subject is in CR or CRi (including CRp).

If a subject cannot resume AG-120/placebo within 28 days, the subject should be discontinued from study treatment if they have previously discontinued treatment with azacitidine. Other reasons for treatment termination are provided in Section 8.5. If AG-120 or placebo is discontinued, the subject will complete the EOT and Follow-up Visits, and will then enter EFS Follow-up (if the subject has not already experienced an EFS event [eg, treatment failure, relapse, or death]) and subsequent Survival Follow-up. If a dose is delayed, visit days (in cycles/days) will be paused until the next planned study visit (eg, if a dose is held on C3D1, the next scheduled visit when dosing begins again will become C3D1); disease response assessments should continue regardless of dose delays.

Table 1: Management of Adverse Events

Adverse Events (AEs)	Action
Grade 2 nausea or vomiting (related or unrelated)	• Consider holding dose of AG-120/placebo until resolution of AE to Grade <1 within 4 weeks (28 days) of supportive therapy. • Manage with supportive therapy according to the institutional standard of care. • Resume AG-120/placebo at same dose.
Grade 3 AEs (related, first event)	• Hold dose of AG-120/placebo until resolution to Grade <1 or baseline within 4 weeks of supportive therapy and then resume dose. • Manage with supportive therapy according to the institutional standard of care. • If the Grade 3 AE recurs (a second time), hold dose until resolution, and then reduce AG-120/placebo to 250 mg in consultation with the Medical Monitor. Re-escalation may be permitted after discussion with the Medical Monitor. • If the Grade 3 AE recurs (a third time) despite dose reduction of AG-120/placebo, then consider discontinuing AG-120/placebo in consultation with the Medical Monitor.
Grade 4 hematologic AEs (related, first event)	• Hold AG-120/placebo. • Manage with supportive therapy according to the institutional standard of care. • If the AE resolves to Grade ≤1 or baseline within 4 weeks, then restart AG-120/placebo dosing at 250 mg in consultation with the Medical Monitor. Re-escalation may be permitted after discussion with the Medical Monitor. • If the AE does not resolve to Grade ≤1 or baseline within 4 weeks, consider discontinuing study treatment in consultation with the Medical Monitor. • If the Grade 4 AE recurs (a second time), despite dose reduction, hold dose until resolution. AG-120/placebo should be discontinued in consultation with the Medical Monitor.
Grade 4 non-hematologic AE (related)	• Discontinue AG-120/placebo.

Refer to Section 9.9 for management of AESIs for AG-120.

If AG-120/placebo is discontinued, the subject may continue treatment with azacitidine on study.

If the Investigator suspects that a subject has PML, treatment with AG-120/placebo should be suspended until a diagnosis of PML has been ruled out.

9.8.2. Azacitidine Dose Modifications and Stopping Criteria

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

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

The initiation of a new cycle will start 21 days after administration of the Day 7 (± 3 days) dose of azacitidine if administered over 7 continuous days or 19 days after the Day 9 (± 3 days) dose if administered on a 5-2-2 schedule. The initiation of a new cycle will start upon the ability to reinitiate combination therapy.

If azacitidine is permanently discontinued for non-hematologic or hematologic toxicities, AG-120/placebo may continue at the discretion of the Investigator and with agreement from the Medical Monitor, provided that the subject is in CR or CRi (including CRp) and needs to discontinue azacitidine due to protocol-specified azacitidine-related toxicity (eg, delayed bone marrow recovery).

9.8.2.1. Azacitidine Dose Modifications due to Non-Hematologic Toxicity

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

9.8.2.2. Azacitidine Dose Modifications due to Hematologic Toxicity

Treatment with azacitidine is associated with anemia, neutropenia, and thrombocytopenia, particularly during the first 2 cycles. Complete blood counts should be performed as specified in the Schedule of Assessments (Table 6), and as needed to monitor toxicity.

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

For example, if the baseline, pre-cycle neutrophil count is 500×10^9/L and the Nadir count is 100×10^9/L, recovery is defined as: ≥100 + (0.5 [500 − 100]), $\geq 300 \times 10^9$/L.

Subjects without reduced baseline blood counts (ie, WBC count >3.0 × 10^9/L, ANC >1.5 × 10^9/L, and platelets >75.0 × 10^9/L) prior to first treatment:

If hematologic toxicity is observed following azacitidine treatment, the next cycle of azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 2 weeks (14 days), no dose adjustment is necessary. However, if recovery has not been achieved within 2 weeks, the azacitidine dose should be reduced according to Table 2. Following dose modifications, the cycle duration should return to 4 weeks (28 days). The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops). A flow diagram for the determination of azacitidine dose adjustment in subjects without reduced baseline blood counts is provided in Appendix 15.4.

Table 2: Hematologic Dose Reductions for Azacitidine Based on Absolute Neutrophil Count and Platelets

Nadir Counts		% Dose in the next course if recovery[a] is not achieved in next 2 weeks (14 days)
ANC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	
≤ 1.0	≤ 50	50%
> 1.0	> 50	100%

Abbreviations: ANC = absolute neutrophil count.
a Recovery = counts ≥ nadir count + (0.5 × [baseline count − nadir count]).

Subjects with reduced baseline blood counts (ie, WBC count ≤3.0 × 10^9/L or ANC ≤1.5 × 10^9/L or platelets ≤75.0 × 10^9/L) prior to treatment:

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

If the decrease in WBC count, ANC, or platelets is greater than 50% from the value prior to treatment, with no improvement in cell line differentiation, the next cycle of azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 2 weeks, no dose adjustment is necessary. However, if recovery has not been achieved within 2 weeks, bone marrow cellularity should be determined. If the bone marrow cellularity is >50%, no dose adjustments should be made. If bone marrow cellularity is ≤50%, azacitidine treatment should be delayed and the dose reduced according to Table 3.

Table 3: Hematologic Dose Reductions for Azacitidine Based on Bone Marrow Cellularity

Bone Marrow Cellularity	% Dose in the next course if recovery[a] is not achieved in next 2 weeks (14 days)	
	Recovery ≤3 weeks	Recovery >3 weeks
15% to 50%	100%	50%
< 15%	100%	33%

[a] Recovery = counts ≥ nadir count + (0.5 × [baseline count - nadir count]).

Following azacitidine dose modifications, the cycle duration should return to 4 weeks (28 days). The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops). A flow diagram for the determination of azacitidine dose adjustment in subjects with reduced baseline blood counts is provided in Appendix 15.4.

9.8.2.3. Azacitidine Therapy and Renal Dysfunction

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported rarely in subjects treated with IV azacitidine in combination with other chemotherapeutic agents. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mmol/L in association with an alkaline urine and hypokalemia (serum potassium <3 mmol/L) developed in 5 subjects with chronic myelogenous leukemia treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate (< 20 mmol/L) occur, the dose should be reduced by 50% on the next course. Similarly, if unexplained elevations in

serum creatinine or blood urea nitrogen (BUN) to ≥2-fold above baseline values and above ULN occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle. The reduced dose of azacitidine should be maintained during subsequent cycles that are given (unless toxicity develops).

The main excretion route of azacitidine is through the urine; additional caution is warranted if renal impairment is present at baseline.

AG-120/placebo should continue to be taken if azacitidine is interrupted beyond the 4-week (28-day) cycle as long as daily AG-120/placebo dosing is not believed, in the opinion of the Investigator, to have been part of the reason for interruption.

9.9. Adverse Events of Special Interest for AG-120

The following are guidelines for the management of AESIs based on the nonclinical and clinical safety findings for AG-120.

9.9.1. QT Prolongation

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

Prolongation of heart-rate corrected QT interval using Bazett's method has been observed in monkeys at relatively high doses of AG-120 and has been identified as an expected risk of treatment with AG-120 (see the IB). Events of QT prolongation (ie, QTcF Grade ≥3 should be reported as AESIs to the Sponsor within 24 hours, according to expedited reporting procedures (see Section 11.2.3).

Subjects may be at increased risk for the development of QT prolongation when treated with AG-120 in combination with fluoroquinolones, azole antifungal agents, or serotonin ($5\text{-}HT_3$) antagonists. Investigators must be vigilant; refrain from administering concomitant medications associated with QT prolongation and if no other therapeutic options are available, monitor subjects receiving study treatment with the combination of these drugs and evaluate ECG and electrolytes (including potassium, magnesium, and calcium), particularly in subjects presenting with nausea, vomiting, or diarrhea. Systemic administration of a moderate or strong CYP3A4 inhibitor requires careful monitoring of QTcF.

Subjects who experience QT prolongation (ie, QTcF >480 msec; NCI CTCAE Grade ≥2) while receiving study treatment should be promptly evaluated for causality of the QT prolongation and managed according to the following guidelines and Table 4:

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects.
- If no other cause is identified and the Investigator believes it is appropriate, particularly if QTcF remains elevated (after the above measures have been implemented, or as determined by the Investigator), study treatment may be interrupted, and an ECG should be rechecked in approximately 1 week after the QT prolongation event was first observed or more frequently as clinically indicated. If

QTcF has recovered or improved and the Investigator believes it is safe to do so, re-challenge with study treatment should be considered if held. Dose adjustments or interruptions for QTcF prolongation in the context of a pre-existing bundle branch block should be discussed with the Medical Monitor. Recommendations may deviate from Table 4 depending on the clinical context and the adjusted QTcF value. Consultation with a cardiologist is recommended in these circumstances.

- ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTcF reduction to ≤480 msec.

Table 4: Management of QT Prolongation by NCI CTCAE Grade

NCI CTCAE Grade	Management
Grade 2 (QTcF >480 and ≤500 msec)	• The dose of study treatment may be reduced to 250 mg QD without interruption of dosing. The dose of study treatment may be re-escalated to the prior dose in ≥2 weeks (14 days) after QT prolongation has decreased to ≤Grade 1.
Grade 3 (QTcF >500 msec on at least 2 separate ECGs)	• Hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. • Monitor electrolyte levels and supplement with electrolytes as clinically indicated. • Review and adjust concomitant medications with known QT prolongation effects. • Dosing with study treatment will be interrupted. If QTcF returns to within 30 msec of baseline or <470 msec within 2 weeks, treatment may be resumed at a reduced dose of 250 mg QD. • The dose of study treatment cannot be re-escalated following dose reduction for Grade 3 QT prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.
Grade 4 (QTcF >500 msec or >60 msec change from baseline with Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	• Subjects should be admitted to a hospital for continuous cardiac monitoring and discharged only after review by a cardiologist. • Dosing with study treatment should be permanently discontinued.

Abbreviations: NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once daily; QTcF = heart-rate corrected QT interval using Fridericia's method.
Note: Per NCI CTCAE, version 4.03.

9.9.2. IDH Differentiation Syndrome

Events of IDH differentiation syndrome have been reported in subjects with hematologic malignancies in Study AG120-C-001 during treatment with AG-120 (see the IB). Any event of differentiation syndrome assessed as Grade ≥2, irrespective of seriousness, should be reported to the Sponsor as an AESI within 24 hours (see Section 11.2.3).

Subjects treated with AG-120 have developed signs and symptoms of differentiation syndrome. Clinical features may include some or all of the following: unexplained fever, skin rash, hypoxia, respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion,

weight gain, and clinical deterioration. Laboratory features may include an increase in ANC and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered per se as diagnostic of the syndrome, and other causes should be sought and excluded. If IDH Differentiation Syndrome is suspected, and is Grade ≥2, Investigators must report the suspected diagnosis as the AE: IDH Differentiation Syndrome.

Any event of IDH Differentiation Syndrome assessed as Grade ≥2 should be reported to the Sponsor as either an SAE or AESI depending on the clinical assessment of seriousness.

It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected IDH differentiation syndrome:

- Temporary hold of AG-120/placebo if clinical features cannot be medically managed with the following:
  - Control of leukocytosis with hydroxyurea (see Section 9.13.4.3)
  - Prompt administration of corticosteroids at a suggested dose of 10 mg of dexamethasone IV every 12 hours until disappearance of symptoms and signs, and for a minimum of 3 days
  - Initiation of furosemide, if clinically required
  - Prompt initiation of leukapheresis, if required

Immediate communication with the Medical Monitor is encouraged for guidance regarding treatment. Once the signs and symptoms resolve and the subject's clinical condition improves, AG-120/placebo may be reinitiated if study treatment was held. The dose of AG-120/placebo at reinitiation is to be discussed with the Medical Monitor.

9.9.3. Leukocytosis

Events of leukocytosis have been reported in subjects with hematologic malignancies in Study AG120-C-001 during treatment with AG-120 (see the IB). Any event of leukocytosis assessed as Grade ≥3, irrespective of seriousness, should be reported to the Sponsor as an AESI within 24 hours (see Section 11.2.3).

See Section 9.13.4 for guidance on the use of hydroxyurea in the event of leukocytosis.

The following guidelines must be used when grading the AE of leukocytosis:

NCI CTCAE Grade	Absolute Neutrophil Count/Clinical Manifestation Hydroxyurea Regimen
Grade 3	> 100,000/mm^3
Grade 4	Clinical manifestations of leukostasis; urgent intervention indicated
Grade 5	Death

Note: Per National Cancer Institute (NCI) Common Terminology for Adverse Events Criteria (CTCAE), version 4.03.

9.10. Other Potential Risks

9.10.1. Leukoencephalopathy

Leukoencephalopathy is a potential risk associated with AG-120 treatment based on clinical safety findings observed across the AG-120 clinical development program. Progressive multifocal leukoencephalopathy and posterior reversible encephalopathy syndrome (PRES), both Grade 3 SAEs, have each been reported in 1 subject.

The signs and/or symptoms of PML may begin gradually, usually worsen rapidly, and vary depending on which part of the brain is infected. Signs and symptoms may include difficulty with walking and other movements, progressive weakness, decline in mental function, visual field deficits, and speech and language disturbances. Rarely, headaches and seizures occur. Subjects should be monitored for onset of signs or symptoms suggestive of PML. Diagnostic evaluations may include consultation with a neurologist, magnetic resonance imaging (MRI) of the brain, lumbar puncture, and/or brain biopsy as clinically warranted. The Investigator should immediately contact the Study Medical Monitor when PML is a suspected or confirmed diagnosis. Treatment with AG-120/placebo should be suspended in the setting of suspected PML and permanently discontinued in subjects with confirmed PML. Subjects with a prior history of PML should not be treated with AG-120 and are excluded from this study.

Posterior reversible encephalopathy syndrome is a rare clinic-radiological neurological syndrome (Linda and von Heijne, 2015). Clinical characteristics may include subacute onset of headache, hypertension, seizures, altered mental status, visual disturbances, and occasionally other focal neurological signs. Radiologically, signs of vasogenic edema are usually seen bilaterally in the white matter of the parieto-occipital lobes, but changes can also be seen in frontal and temporal lobes, brainstem, cerebellum, and in cortical as well as deep gray matter. Subjects should be monitored for onset of neurological signs and/or symptoms that are clinically associated with PRES. Diagnostic evaluations may include consultation with a neurologist, MRI of the brain, and other recognized standard of care measures as clinically warranted. Additionally, the Investigator should consult with the Study Medical Monitor for management guidelines to be utilized in the setting of suspected or confirmed PRES.

Refer to the AG-120 IB for further details on these events.

9.10.2. Sensorimotor Neuropathy/Polyneuropathy

Sensorimotor neuropathy/polyneuropathy is a potential risk associated with AG-120 treatment based on safety findings observed across the AG-120 clinical development program. Guillain-Barre syndrome are rare, serious syndromes that affect the central and peripheral nervous systems.

Subjects should be monitored for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. If a subject experiences signs or symptoms suggestive of sensorimotor neuropathy, Guillain-Barre syndrome, or lumbosacral plexopathy, diagnostic evaluation may include a consultation with a neurologist, lumbar puncture, and electromyography. The Investigator should immediately contact the Study Medical Monitor when Guillain-Barre syndrome is a suspected or confirmed

diagnosis. AG-120/placebo should be permanently discontinued in subjects with a confirmed diagnosis of Guillain-Barre syndrome.

Refer to the AG-120 IB for further details on these events.

9.10.3. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potential risk associated with AG-120 treatment based on clinical safety findings in subjects with hematologic malignancies. Refer to the AG-120 IB for further details on events of TLS.

Tumor lysis syndrome was observed in 19 (7.4%) subjects with advanced hematologic malignancies in Study AG120-C-001, 2 (3.3%) subjects with newly diagnosed AML in Study AG120-221-C-001, and 1 (4.3%) subject with newly diagnosed AML in Study AG-221-AML-005. No events of TLS have been reported in Study AG120-C-009, Studies AG120-C-002 and AG120-C-005 in solid tumors, or in clinical pharmacology studies.

Development of TLS is a known risk associated with AML. Clinical risk factors include leukocytosis (with or without disease progression) and concurrent use of cytoreductive agents, such as hydroxyurea. AG-120 can induce myeloid proliferation resulting in a rapid reduction in tumor cells, which may pose a risk for tumor lysis syndrome. In some instances, TLS events occurred in subjects who also had rising WBC counts, suggesting the possibility that these events were related to the underlying malignancy or were co-occurring with IDH differentiation syndrome. Prophylactic and treatment measures for TLS should be employed as clinically indicated.

9.11. Duration of Subject Participation

9.11.1. Treatment Duration

Daily treatment with AG-120 + azacitidine or placebo + azacitidine will begin on the first day of Cycle 1. Subjects should be treated for a minimum of six 4-week (28-day) cycles of combination therapy. With Medical Monitor approval, subjects may continue to receive:

- AG-120 or placebo following discontinuation of azacitidine, provided that they are in CR or CRi (including CRp) and need to discontinue azacitidine due to protocol-specified azacitidine-related toxicity (eg, delayed bone marrow recovery), or
- Azacitidine following discontinuation of AG-120 or placebo, provided that they have not met the definition of disease relapse or progressive disease.

Subjects should continue to receive study treatment until disease relapse, disease progression, treatment failure, development of an unacceptable toxicity (AE), confirmed pregnancy, withdrawal by subject, protocol violation, death, or End of Study.

Subjects with a response less than CR at 24 weeks or beyond can continue on treatment if demonstrating treatment benefit, defined as any of the following: 1) Transfusion-independence while on study treatment; 2) ANC >500/µL; or 3) platelets >50,000/µL.

Following discontinuation of study drug, subjects are to attend a Follow-up Visit 4 weeks (28 days) after the last dose of study drug for final assessments. When study drug is withheld from a subject in order to resolve a toxicity and the subject does not subsequently restart

treatment, EOT is defined as the date when the study drug was first held. Subjects should proceed with EOT assessments, safety assessments, and EFS/Survival Follow-up. If the decision not to restart study treatment occurs outside of the 4-week Safety Follow-up window, the subject should proceed with EFS/Survival Follow-up.

All subjects who discontinue study treatment without experiencing any 1 of the following: death, disease relapse, treatment failure, or withdrawal of consent, will be followed every Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter for EFS until they experience treatment failure, relapse, death, withdraw from the study, or until the time when 173 EFS events have occurred or as deemed necessary by the IDMC.

Once the study is unblinded, survival follow up will continue. All subjects who are alive after an EFS event will be contacted every 8 weeks for survival follow-up until death, withdrawal by subject, loss to follow-up, or when the Sponsor ends the study.

9.11.2. End of Study

At the time of primary endpoint analysis (approximately 173 EFS events or as deemed necessary by the IDMC), the study will be unblinded. Subjects on treatment at that time may continue receiving study drug. After unblinding, and if the benefit-risk profile favors treatment, subjects randomized to placebo may be offered the choice to receive AG-120. End of Study is defined as the time at which all subjects have died, discontinued the study, are lost to follow-up, or have withdrawn consent; or when the Sponsor ends the study.

9.11.3. Treatment Compliance

Subjects will be dispensed the appropriate number of Sponsor-packaged, labeled bottle(s) for 4 weeks (28 days) of dosing on Day 1 (± 3 days) of each 4-week (28-day) cycle; alternatively, subjects may be dispensed the appropriate number of bottle(s) needed until the next study visit. The subject will be asked to return all bottles and unused tablets (or empty bottles) on Day 1 (± 3 days) of each cycle or at their next study visit for assessment of compliance with the dosing regimen.

Subjects will receive instructions for home administration of study treatment along with a diary to record the date and time of each dose, as well as the number of tablets taken (see Section 9.12).

Site staff will administer all doses of azacitidine when given as study drug.

9.12. Study Drug Accountability

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

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and return to the Sponsor or its designee (or disposal of the drug, if approved by the Sponsor). These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study treatment received from the Sponsor. Accountability records will

include dates, quantities, batch/serial numbers, expiration dates (if applicable), and subject numbers. The Sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

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

Subjects will receive instructions for home administration of study treatment along with a diary to record the date and time of each dose, as well as the number of tablets taken.

All unused and used study treatment should be retained at the site until they are inventoried and verified by study site personnel and/or the study monitor. All used, unused, or expired study treatment will be returned to the Sponsor or its designee or if authorized, disposed of at the study site per the site's Standard Operating Procedures (SOPs), and documented. All material containing AG-120 and/or matched placebo will be treated and disposed of as hazardous waste in accordance with governing regulations.

9.13. Prior and Concomitant Medications and Treatments

9.13.1. Prior Medications and Procedures

All medications administered and procedures conducted within 4 weeks (28 days) prior to the first day of study drug administration (C1D1) are to be recorded in the eCRF.

As available, transfusion history, including RBC and platelet transfusion, for up to 56 days prior to C1D1 should be recorded at the Screening visit. This documentation should include dates of each transfusion and units administered.

9.13.2. Concomitant Therapy Requiring Careful Monitoring

Concomitant use of drugs with a potential for QT prolongation should be avoided and replaced with alternative treatments. If this is not possible, subjects receiving these drugs should be adequately monitored by ECG controls, drug concentration (where applicable), and serum electrolytes (ie, potassium and magnesium). See Section 9.9.1 for guidance on managing QT prolongation.

These medications include, but are not limited to:

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

Other examples of drugs known to prolong the QT interval are listed in Appendix 15.5.

Systemic administration of moderate or strong CYP3A4 inhibitors (see Appendix 15.7) requires careful monitoring of QTcF.

Coadministration of AG-120 with narrow therapeutic index drugs that are extensively metabolized by CYP2C9 (eg, phenytoin, warfarin) may result in decreased concentrations of these drugs. Consider alternative therapies that are not sensitive substrates of CYP2C9 during

treatment with AG-120. Subjects should be monitored for loss of therapeutic effect of these medications if coadministration with AG-120/placebo cannot be avoided. Monitor international normalized ratio (INR) levels more frequently in subjects receiving warfarin during initiation or discontinuation of AG-120/placebo.

Coadministration of AG-120 may decrease the concentrations of hormonal contraceptives. Consider alternative methods of contraception in subjects receiving AG-120/placebo. Please refer to Inclusion Criterion 10 in Section 8.2 for contraception requirements.

9.13.3. Concomitant Therapy to be Avoided

The following therapies are contraindicated during the study while subjects are receiving study drug:

- Strong CYP3A4 inducers listed in Appendix 15.6, unless the subject can be transferred to other medications within ≥5 half-lives prior to dosing.
- Sensitive CYP3A4 substrate medications with narrow therapeutic windows listed in Appendix 15.6, unless the subject can be transferred to other medications within ≥5 half-lives prior to dosing.
- Anticancer therapy other than the treatment outlined in the protocol is not permitted while subject is receiving study treatment, with the exception of hydroxyurea as described in Section 9.13.4.3. If alternative therapy is required for treatment of the subject's disease, the subject should be discontinued from the study treatment.

The above listed medications will be allowed during the EFS and Survival Follow-up periods.

9.13.4. Allowed Concomitant Therapy

Medications and treatments other than those specified above are permitted during the study. All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care. Subjects should receive analgesics, antiemetics, anti-infectives, antipyretics, and blood products as necessary. Subjects may also receive antimicrobial prophylaxis as necessary.

9.13.4.1. Neutropenia Therapeutics

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

9.13.4.2. Antimicrobial Prophylaxis

Subjects should receive antimicrobial prophylaxis (NCCN, 2018). Subjects may be at increased risk for the development of QT prolongation when treated with ivosidenib in combination with known QT prolonging drugs like fluoroquinolones, azole antifungal agents, or serotonin (5-HT3) antagonists (see Section 11.2.3.1).

9.13.4.3. Leukocytosis Prophylactics and Therapeutics (Hydroxyurea)

It is recommended that the prophylactic and therapeutic measures indicated below are undertaken at the earliest manifestations of leukocytosis:

- Temporary hold of study treatment only if symptoms cannot be medically managed with the following:
  - Prompt initiation of hydroxyurea at up to a dose of 2000 or 3000 mg PO BID
  - Prompt initiation of leukapheresis, if required

Treatment with hydroxyurea is allowed during treatment with AG-120/placebo + azacitidine for control of peripheral leukemic blasts in subjects with leukocytosis (WBC >30,000/µL). Treatment with hydroxyurea prior to randomization is allowed (Table 5).

Immediate communication with the Medical Monitor during active management of leukocytosis is required. Once the signs and symptoms resolve and the subject's clinical condition improves, AG-120/placebo may be reinitiated if study treatment was held. The dose of AG-120/placebo at reinitiation is to be discussed with the Medical Monitor.

Table 5: Recommended Initial Doses of Hydroxyurea for Management of Leukocytosis

Hydroxyurea Dose and Regimen	Total White Blood Cell Count (/µL)	Absolute Increase in Total White Blood Cell Count from Baseline (/µL)
1000 mg QD	25,000 to 50,000	15,000 to 29,000
2000 mg BID	51,000 to 75,000	30,000 to 49,000
3000 mg BID	≥ 76,000	≥ 50,000

Abbreviations: QD = once daily, BID = twice daily.

9.13.4.4. Steroids

Steroids are allowed for the treatment of IDH Differentiation Syndrome, if warranted, as standard of care (and may be used prior to randomization).

All concomitant therapies, including any procedures performed during the study, transfusions of blood products (see Section 10.8.2), and medications used to treat AEs, are to be reported on the eCRF.

9.13.4.5. Capturing Concomitant Therapies Post-Treatment

Only new anticancer therapies are required to be captured in the eCRF during the EFS and Survival Follow-up periods.

10. STUDY ASSESSMENTS

10.1. Schedule of Assessments

Table 6 provides the Schedule of Assessments for all subjects enrolled in the study, while Table 7 summarizes the PK sampling time points and Table 8 summarizes the PD sampling time points. A detailed description of study assessments follows these tables.

After providing written informed consent, subjects will undergo Screening evaluations. The Screening Visit is to be conducted within 4 weeks (28 days) prior to randomization; however, the IDH1m Prescreening can be conducted prior to the 28-day Screening window. All Screening procedures should be complete prior to first study drug administration. Subjects are to attend study center visits as outlined in the Schedule of Assessments (see Table 6).

Study center visits will be conducted on an outpatient basis whenever possible. Study visits should occur on the scheduled visit day; a ± 3-day window (± 7 days for bone marrow aspirate/biopsy, peripheral blood sampling for IDH-mutated cells/leukemic blasts, and evaluation of disease status) is allowed to accommodate subjects' schedules. Bone marrow evaluations and peripheral blood counts for response assessments should be performed within 1 day of each other.

An EOT Visit will be conducted as soon as possible after discontinuing both (or the second discontinued treatment if the 2 study treatments are discontinued on different days) study treatments (within 1 week of the last dose of study drug); in addition, subjects are to attend a Follow-up Visit 4 weeks after the last dose of study drug for final assessments. If a subject's dose is held and it is subsequently decided to discontinue treatment, the EOT Visit should be conducted as soon as possible, but no later than 4 weeks after the last dose of study drug.

All subjects who discontinue study treatment without experiencing any 1 of the following: death, disease relapse, treatment failure, or withdrawal of consent, will be followed every Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter for EFS until they experience treatment failure, or relapse, or death, or withdrawal of consent, or until the time when 173 EFS events have occurred or as deemed necessary by the IDMC.

Once the study is unblinded, survival follow up will continue. All subjects who are alive after an EFS event will be contacted every 8 weeks for survival follow-up until death, withdrawal by subject, loss to follow-up, or when the Sponsor ends the study.

Table 6: Schedule of Assessments

Visit/Cycle:	Screen[1]*	4-Week (28-Day) Treatment Cycles									EOT[2]	4 Weeks Post-Treatment[3]	EFS Follow-up[4]	Survival Follow-up
		Cycle 1				Cycle 2		Cycles 3 & 4		Cycles 5+				
Study Day (±3 days unless otherwise noted) (Weeks):	D −28 to −1 (W −4 to W −1)	D1 (W1)	D8 (W2)	D15 (W3)	D22 (W4)	D1 (W5)	D15 (W7)	D1 (W9, W13)	D15 (W11, W15)	D1 (W17+)				
Informed Consent	X													
Review Eligibility Criteria	X													
Medical and Surgical History	X													
Demographics	X													
IDH1 Mutation Analysis[5]	X													
Buccal Swab[6]	X													
[redacted]														
Randomization[8]	X													
Prior/Concomitant Medications and Procedures	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Event Assessment[9]	X	X	X	X	X	X	X	X	X	X	X	X		
Height, Weight, BSA[10]	X	X				X		X		X				
Vital Signs[11]	X													
Bone Marrow Aspirate/Biopsy[12]	X							X[12]		X[12]	X		X	
Peripheral Blood[13]	X							X[13]		X[13]	X		X	
Evaluate Disease/Response[14]	X							X[14]		X[14]	X		X	

Visit/Cycle:	Screen[1]*	4-Week (28-Day) Treatment Cycles									EOT[2]	4 Weeks Post-Treatment[3]	EFS Follow-up[4]	Survival Follow-up
		Cycle 1				Cycle 2		Cycles 3 & 4		Cycles 5+				
Study Day (±3 days unless otherwise noted) (Weeks):	**D −28 to −1 (W −4 to W −1)**	**D1 (W1)**	**D8 (W2)**	**D15 (W3)**	**D22 (W4)**	**D1 (W5)**	**D15 (W7)**	**D1 (W9, W13)**	**D15 (W11, W15)**	**D1 (W17+)**				
Physical Examination	X (complete exam)	X (limited exam[15])				X (limited exam[15])		X (limited exam[15])		X (limited exam[15])	X (complete exam)			
ECOG Performance Status	X	X				X		X		X	X			
Pregnancy Test[16]	X	X				X		X		X	X			
Hematology, Serum Chemistry[17]	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation Studies[18]	X	X				X		X		X	X			
PK/PD Assessments		See Table 7 for PK sampling schedule and Table 8 for PD sampling schedule												
ECHO/MUGA for LVEF[19]	X													
12-lead ECG[20]	X	X		X		X	X	X		X	X			
Quality of Life Assessment[21]		X		X		X	X	X[21]		X[21]	X	X		
AG-120 Administration[22]		X	X	X	X	X	X	X	X	X				
Azacitidine Administration[23]		See Section 9.7.2 for details												
Subject Diary and Study Medication Accountability[24]		X				X		X		X	X			
Survival[25]														X
Subsequent Anticancer Therapies											X	X	X	X

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BP = blood pressure; BSA = body surface area; BUN = blood urea nitrogen; C1D1 = Cycle 1, Day 1; CR = complete remission; D = Day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EFS = event-free survival; EOT = End of Treatment; ICF = informed consent form; IDH = isocitrate dehydrogenase; IDH1 = isocitrate dehydrogenase 1; IV = intravenous; LVEF = left ventricular ejection fraction; MUGA = multi-gated acquisition; PD = pharmacodynamic; PK = pharmacokinetic; QD = once daily; RBC = red blood cell; SAE = serious adverse event; SC = subcutaneous; W = week; WBC = white blood cell.

* Subjects may sign a pre-Screening ICF to allow for collection of a bone marrow and peripheral blood sample for central IDH1 and [redacted] prior to the 4-week (28-day) Screening window. Bone marrow biopsy/aspirate and peripheral blood samples must be sent with proof of shipment to the central laboratory as part of Pre-screening to satisfy the Screening time points for these sample types, as long as they are collected within 28 days prior to randomization.

1 Screening assessments that may have been conducted prior to informed consent but within 28 days of C1D1 need not be repeated and results may be entered into the eCRF.

2 All subjects are to undergo an EOT assessment within 1 week of the last dose of study treatment (AG-120/placebo and azacitidine). If a subject discontinues study treatment at a regularly scheduled visit, EOT assessments may be performed at that visit. Subjects' eligibility to cross over to AG-120 + azacitidine after Sponsor unblinding of the study will be determined based on procedures conducted in the EOT Visit.

3 All subjects are to have a post-treatment visit 4 weeks (±3 days) after the last dose of study treatment (AG-120/placebo and azacitidine).

4 All subjects who discontinue study treatment without experiencing any 1 of the following: death, disease relapse, treatment failure, or withdrawal of consent, will be followed every Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter for EFS until they experience treatment failure, relapse, death, withdraw from the study, or until the time when 173 EFS events have occurred or as deemed necessary by the IDMC.

5 Screening bone marrow aspirate (or peripheral blood sample if bone marrow aspirate is not available, with Medical Monitor approval) will be collected for central confirmation of IDH1-mutated disease prior to randomization, and can be conducted before the 28-day Screening window.

6 A buccal swab for germ-line mutation analysis will be obtained at Screening.

[redacted]

8 Subjects should start study treatment (ie, C1D1 [Week 1]) within 3 days (72 hours) of randomization.

9 Prior to first dose of study treatment, only AEs that are classified as SAEs deemed related to study procedures should be reported. After initiation of study drug, all AEs and SAEs, regardless of attribution, will be collected. Subjects will be assessed at the Follow-up Visit (4 weeks post-treatment) to determine if any new AEs have occurred. After this period, Investigators should report only SAEs that are considered to be related to study treatment (AG-120/placebo or azacitidine).

10 Height at Screening only. Weight and body surface area calculation should be conducted on Day 1 of each cycle, prior to dosing.

11 Vital signs (temperature, BP [sitting for 5 minutes], pulse rate, respiratory rate) are to be taken at Screening and at any point when abnormal vital signs are suspected. All clinically relevant abnormal vital sign results will be reported as AEs.

12 A bone marrow aspirate (and biopsy if standard of care, or in case of a dry tap or aspicular [diluted] sample) is required at: Screening (if a sample was collected and submitted as part of Pre-screening within 28 days prior to randomization, an additional Screening sample is not required); Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter; at EOT; during EFS follow-up (samples should continue being collected during EFS according to the same schedule that was used when the subject had the EFS event; bone marrow samples are optional during EFS follow-up for post-transplant subjects); as dictated by physical exam and/or blood counts; and/or any time that disease progression is suspected. At EOT, a bone marrow aspirate will be collected if it has not been collected within the prior 8 weeks. Upon Sponsor unblinding, bone marrow aspirate will no longer be collected. [redacted] Blood draws for regular hematology assessments and associated CBC results (footnote 17) should be reviewed for the need to evaluate disease status at an unscheduled time point.

13 Peripheral blood for IDH-mutated cells/leukemic blasts is required to be sampled at any time a bone marrow aspirate/biopsy is performed to assess for potential clinical activity. These time points include: Screening (if a sample was collected and submitted as part of Pre-screening within 28 days prior to randomization, an additional Screening sample is not required); Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter; at EOT; during EFS follow-up on the same schedule; as clinically indicated; and/or any time that disease progression is suspected. [redacted] Blood draws for regular hematology assessments and associated CBC results (footnote 17) should be

reviewed for the need to evaluate disease status at an unscheduled time point.

[14] Evaluation of disease status, including evaluation of bone marrow and/or peripheral blood, to be conducted: at Screening (or as part of Pre-screening as long as it is within 28 days prior to randomization); Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter; at EOT; during EFS follow-up on the same schedule; as clinically indicated; and/or any time that disease progression is suspected. Upon Sponsor unblinding, evaluation of disease status will no longer be collected. Subjects are expected to remain on treatment with AG-120/placebo as long as there are no unacceptable toxicities and the subject has a response of at least stable disease. Also includes assessment of transfusions (RBC and platelet), infections, length of any hospital stays, and other efficacy and safety measures that are potentially indicative of clinical benefit. De-identified copies of evaluation reports (bone marrow and/or peripheral blood assessment of disease status) should be submitted. Blood draws for regular hematology assessments (footnote 17) should be reviewed for the need to evaluate disease status at an unscheduled time point.

[15] Clinically directed examinations, including a skin examination.

[16] For female subjects with reproductive potential: A serum β-hCG pregnancy test is required at Screening and must be verified as negative within 72 hours prior to study treatment administration. A urine pregnancy test will be conducted on C1D1 and confirmed negative prior to dosing, and on Day 1 of all subsequent cycles. A urine pregnancy test should be conducted at the end of treatment visit.

[17] Hematology: hemoglobin, RBC count, WBC count with differential, ANC, platelet count, and peripheral blast count. Hematology blood draws should occur prior to administration of any study drugs on visit date.
Chemistry: sodium, potassium, calcium, magnesium, albumin, glucose, BUN, creatinine, lactate dehydrogenase, ALP, AST, ALT, total bilirubin, phosphate, and bicarbonate. Chemistry blood draws should occur prior to administration of any study drugs on visit date.
Blood for hematology and chemistries is to be obtained: at Screening; on Days 1, 8, 15, and 22 (± 3 days) of Cycle 1 (Weeks 1, 2, 3, and 4); on Days 1 and 15 (± 3 days) of Cycles 2, 3, and 4 (Weeks 5, 7, 9, 11, 13, and 15); on Day 1 (± 3 days) of each treatment cycle thereafter (Weeks 17+); at EOT; and 4 weeks post-treatment.

[18] Coagulation: activated partial thromboplastin time (aPTT) at baseline and international normalized ratio (INR). Blood for coagulation studies is to be obtained at Screening, on Day 1 (± 3 days) of each treatment cycle, and at the EOT Visit.

[19] LVEF assessment required within 4 weeks prior to C1D1 (Week 1). ECHO/MUGA should be performed at other times during the study if clinically indicated; if repeated, method (per institutional policy) should be the same throughout the study for the individual subject. Only ECHO may be used at sites in Germany.

[20] Safety ECGs; not central or triplicate. To be obtained at Screening, 4-6 hours post-dose on C1D1 (Week 1) only, and during the visit window on C1D15 (Week 3), C2D1 (Week 5), and C2D15 (Week 7). After Cycle 2, ECGs should be performed on D1 of each cycle and as clinically indicated. An ECG will also be performed at EOT.

[21] Quality of life assessments will occur prior to dosing on Days 1 and 15 (± 3 days) of the first 2 cycles (Weeks 1 and 3 and Weeks 5 and 7); Day 1 (± 7 days) of odd cycles (Weeks 9, 17, 25, etc.); at EOT; and 4 weeks post-treatment. Upon Sponsor unblinding, quality of life assessments will not be conducted.

[22] AG-120/placebo is administered QD beginning on C1D1 (Week 1), prior to administration of azacitidine. If subjects forget to take the daily dose, they should take AG-120 or placebo within 12 hours after the missed dose. Missed doses outside this window or vomited doses should not be taken or repeated.

[23] Azacitidine will be administered SC or IV for 1 week (7 days) of each 4-week (28-day) treatment cycle, starting on Day 1 (± 3 days) of Week 1. A full 7 days of azacitidine is required, but as per institutional practice, a schedule of 5 days of daily doses, followed by no dose received on the weekend and 2 daily doses given again at the start of the next week, is allowed. The same schedule should be used for each subject throughout the duration of treatment, when possible.

[24] Subject diary to be used when subject is an outpatient to record dosing details for AG-120/placebo. While subject is an inpatient, details of AG-120/placebo administration may be captured on subject diary or standard hospital inpatient dosing record. All missed or vomited doses should be noted in the diary. Treatment compliance of AG-120/placebo administration is to be assessed based on return of unused study drug as well as subject diaries. All doses of study drugs (AG-120 or placebo; azacitidine) will be documented in the eCRF, including documentation of any missed doses and dose administered.

[25] Once the study is unblinded, survival follow up will continue. All subjects who are alive after an EFS event will be contacted every 8 weeks for survival follow-up until death, withdrawal by subject, loss to follow-up, or when the Sponsor ends the study.

Table 7: Pharmacokinetic Sampling Schedule

Visit/Cycle:	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycles 3+
Study Day (±3 days) (Week):	**D1 (W1)**	**D8 (W2)**	**D15 (W3)**	**D1 (W5)**	**D1 (W9+)**
Pre-dose[1,2]	X	X	X	X	X
Post-dose					
0.5 hr (±5 min)	X			X	
2 hrs (±15 min)	X			X	
4 hrs (±1 hr)	X			X	

Abbreviations: D = day; hr = hour; min = minute; W = week.

Notes: Blood samples for PK assessments will be drawn pre-dose and at 0.5, 2, and 4 hours post-dose on Day 1 (± 3 days) of Cycles 1 and 2 (Weeks 1 and 5); pre-dose on Days 8 and 15 (± 3 days) of Cycle 1; and pre-dose on Day 1 (± 3 days) of Cycles 3 and beyond (Weeks 9+).

If study drug is not administered on the day of a visit (ie, study drug interruption or permanent discontinuation of study drug), only 1 PK blood sample will be collected.

[1] To be obtained within 30 minutes before dose.

[2] For subjects who cross over, only predose PK samples will be collected.

Table 8: Pharmacodynamic Sampling Schedule

Visit/Cycle:	Cycle 1	Cycle 1
Study Day (±3 days) (Week):	D1 (W1)	D15 (W3)
Pre-dose[1]	X	X

Abbreviations: D = day; W = week.
Note: Blood samples for 2-HG assessment will be drawn at pre-dose on C1D1 and C1D15 (± 3 days).
[1] To be obtained within 30 minutes before dose.

10.2. Informed Consent

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

A complete description of the cytogenetic and IDH1m testing procedures may be presented to potential subjects prior to undergoing cytogenetic and IDH1m testing as part of Pre-screening at any point prior to the 28-day Screening window. Subjects may sign a pre-Screening ICF to allow for collection of a bone marrow and peripheral blood sample for central IDH1 and [redacted] prior to the 4-week (28-day) Screening window. Bone marrow biopsy/aspirate and peripheral blood samples must be sent with proof of shipment to the central laboratory as part of Pre-screening to satisfy the Screening time points for these sample types, as long as they are collected within 28 days prior to randomization.

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

Subject demographic data, including gender, date of birth, age, race, and ethnicity, will be obtained during Screening, according to local regulations.

A complete medical and surgical history, including the type of underlying malignancy and the date of confirmation of the histologic diagnosis of the underlying malignancy, will be obtained during Screening. The medical history is to include all relevant prior medical history as well as all current medical conditions. If available from the medical history, results within the previous 6 months for diffusing capacity of the lungs for carbon monoxide or forced expiratory volume in 1 second will also be recorded.

All medications administered and procedures conducted within 4 weeks (28 days) prior to C1D1 should be recorded in the eCRF.

Red blood cell and platelet transfusion history, including dates of the transfusion and units administered, should be captured for the 56-day period prior to C1D1.

[redacted]

[redacted]

10.5. IDH1 Mutation Analysis

A Screening bone marrow aspirate (or peripheral blood sample if bone marrow aspirate is not available, with Medical Monitor approval) is required for IDH1m confirmation at a central laboratory. IDH1 mutation positivity from either bone marrow aspirate or peripheral blood is required for study eligibility.

With Medical Monitor approval, subjects may be eligible and randomized with local IDH1m testing results; however, bone marrow aspirate for central laboratory testing must have been sent with proof of shipment to the central laboratory prior to randomization. In cases where bone marrow aspirate is not available, peripheral blood samples may be used for IDH1m confirmation with Medical Monitor approval.

A buccal swab for germ-line mutation analysis also will be obtained at Screening in all subjects.

10.6. Safety Assessments

10.6.1. Independent Data Monitoring Committee

Safety data will be reviewed regularly by an IDMC to ensure the safety of the combination therapy. These reviews will occur after the first 6, 12, 24, and 36 subjects have completed 1 cycle of therapy or discontinued, whichever should occur first. Thereafter, safety reviews will be conducted approximately every 6 months until the study is unblinded for the analysis of the primary endpoint. No interim analyses for efficacy are planned.

Members of the IDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The Sponsor will remain blinded to the data until the analysis of the primary endpoint.

All summaries and analyses by treatment arm for the IDMC review will be prepared by an independent data coordinating center. The safety data will include demographic data, AEs, SAEs, and relevant laboratory data. Following their data review, the IDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.

The requirements of these reviews will be specified in the IDMC charter.

10.6.2. Physical Examination and ECOG Performance Status

A complete physical examination, including assessment of weight and body surface area calculation, will be performed at Screening and at the EOT Visit. Height will be obtained at the Screening Visit. A limited physical examination (clinically directed based on signs and symptoms) will be performed on Day 1 (± 3 days) of each cycle. A skin examination as part of the complete and limited physical examination must be performed. After Screening, clinically significant physical examination findings are captured as AEs.

Determination of ECOG PS will be performed at Screening, on Day 1 (± 3 days) of each treatment cycle, and at the EOT Visit. See Appendix 15.8 for ECOG PS scoring.

10.6.3. Vital Signs

Vital signs, including systolic and diastolic BP, heart rate, respiratory rate, and temperature, will be obtained at Screening and at any point abnormal vital signs are suspected. All clinically relevant abnormal vital sign results will be reported as AEs.

10.6.4. Electrocardiogram and Assessment of Left Ventricular Ejection Fraction

The 12-lead ECGs (safety; not central or triplicate) are to be obtained at Screening, 4-6 hours post-dose on C1D1 (Week 1) only and during the visit window on C1D15 (Week 3), C2D1 (Week 5), and C2D15 (Week 7). After Cycle 2, ECGs should be performed on Day 1 of each cycle and as clinically indicated. An ECG will also be performed at EOT. Local ECGs should remain stored at the local site as local source documentation.

All 12-lead ECGs should be obtained following 3 minutes of recumbency or semi-recumbency.

All subjects are to have LVEF determined by ECHO or MUGA scan within 4 weeks prior to C1D1 (Week 1); repeat assessments should be performed at other times during the study if clinically indicated. Method should be per institutional practice and the same method should be used for any subsequent examinations for the individual subject. Sites in Germany may not use MUGA and must use ECHO for LVEF assessments.

10.6.5. Safety Laboratory Assessments

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

Clinical laboratory evaluations are to be conducted according to the Schedule of Assessments (6). In addition, all clinically significant laboratory values will be further investigated according to the judgment of the Investigator.

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

Hematology: Hemoglobin, RBC count, WBC count with differential, ANC, platelet count, peripheral blast count

Chemistry: Sodium, potassium, calcium, magnesium, albumin, glucose, BUN, creatinine, lactate dehydrogenase, ALP, AST, ALT, total bilirubin, phosphate, bicarbonate

Coagulation Studies: Activated partial thromboplastin time (aPTT), INR

Blood for hematology and chemistries is to be obtained: at Screening; on Days 1, 8, 15, and 22 (± 3 days) of Cycle 1 (Weeks 1, 2, 3, and 4); on Days 1 and 15 (± 3 days) of Cycles 2, 3, and 4 (Weeks 5, 7, 9, 11, 13, and 15); on Day 1 (± 3 days) of each treatment cycle thereafter (Weeks 17+); at EOT; and at 4 weeks post-treatment. All blood samples for hematology and chemistries must be drawn prior to administration of study drugs.

Blood for coagulation studies is to be obtained at Screening, on Day 1 (± 3 days) of each treatment cycle, and at the EOT Visit.

Pregnancy Test: All women of reproductive potential must have a negative pregnancy test to be eligible. A serum β-hCG pregnancy test will be performed at Screening and must be confirmed negative within 72 hours prior to study treatment administration.

10.6.6. Adverse Events

All AEs will be graded using the NCI CTCAE version 4.03 grading system (see Appendix 15.9).

Complete details on AE monitoring are provided in Section 11.

10.7. Bone Marrow Samples and Peripheral Blood Leukemic Blast Cells

A bone marrow aspirate (and biopsy if standard of care, or in case of a dry tap or aspicular [diluted] sample) is required at: Screening (if a sample was collected and submitted as part of Pre-screening within 28 days prior to randomization, an additional Screening sample is not required); Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter; at

EOT; during EFS follow-up (samples should continue being collected during EFS according to the same schedule that was used when the subject had the EFS event bone marrow samples are optional during EFS follow-up for post-transplant subjects); as dictated by physical exam and/or blood counts; and/or any time that disease progression is suspected. [redacted] Bone marrow assessments obtained for the evaluation of clinical activity will be collected. De-identified copies of evaluation reports (bone marrow and/or peripheral blood assessment of disease status) should be submitted.

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

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

Bone marrow core biopsies and/or aspirates are to be evaluated for morphology and for karyotype to assess potential disease prognosis (see Section 10.8).

Peripheral blood for IDH1m cells/leukemic blasts is required at any time a bone marrow aspirate/biopsy is performed to assess potential clinical activity (see Section 10.8).

[redacted]

Instructions for the collection, processing, storage, and shipment of samples for central analysis will be provided in a separate study manual. Samples at progression will be stored for potential further [redacted].

10.8. Efficacy Assessments

10.8.1. Response to Treatment

The efficacy of AG-120 will be evaluated by Investigator-assessed response to treatment based on modified IWG Response Criteria for AML and ELN guidelines, including assessment of the following (see Table 10):

- EFS is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by Week 24. Subjects who do not achieve CR by Week 24 will be considered to have had an event at Day 1 of randomization. For the remaining CR responders, the event time will be the time of either disease relapse or death, whichever occurs first.
- CR is defined as bone marrow blasts <5% and no Auer rods; absence of extramedullary disease; ANC $\geq 1.0 \times 10^9$/L (1000/µL); platelet count $\geq 100 \times 10^9$/L (100,000/µL); and independence of red blood cell transfusions.

- CRh is defined as a CR with partial recovery of peripheral blood counts (< 5% bone marrow blasts, platelets >50,000/µL, and ANC >500/µL). CRh will be derived by the Sponsor.
- ORR is defined as the rate of CR, CRi (including CRp), PR, and MLFS. The best response is calculated using the following order: 1) CR; 2) CRi (including CRp); 3) PR, and 4) MLFS.

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

Treatment decisions will be based on Investigator's assessment.

Subjects will have the extent of their disease assessed and recorded: at Screening (or as part of the Pre-screening process, as long as it is within 28 days prior to randomization); Day 1 (± 7 days) of Weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter; at EOT; as dictated by physical exam and/or blood counts; and/or any time that disease progression is suspected. For subjects who discontinue treatment prior to disease progression, disease assessments will be performed on the same schedule until disease progression/relapse.

Subjects will also be evaluated for their RBC and platelet transfusion requirements, including dates of the transfusion(s) and number of units administered, at each disease response assessment.

The criteria outlined in Table 10 and Table 11 will be used to assess response to treatment.

Table 10: Modified International Working Group Response Criteria for Acute Myeloid Leukemia

Category	Definition
Complete remission (CR)[a]	Bone marrow blasts <5% and no Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/µL); platelet count ≥100 × 10^9/L (100,000/µL); independence of red blood cell transfusions
CR with incomplete recovery (CRi), including CR with incomplete platelet recovery (CRp)[b]	All CR criteria except for residual neutropenia (ANC <1.0 × 10^9/L [1000/µL]) or thrombocytopenia (platelet counts <100 × 10^9/L [100,000/µL]; without platelet transfusion for at least 1 week prior to disease assessment)
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5% and no Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5%-25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Relapse (defined only for subjects who have previously attained CR, CRi, CRp, or MLFS)[c]	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease

Source: (Cheson et al, 2003; Döhner et al, 2017; Sievers et al, 2001).
Abbreviations: AML = acute myeloid leukemia; ANC = absolute neutrophil count; IWG = International Working Group; MDS = myelodysplastic syndrome.
Note: Modified to remove molecular complete remission (CRm) and cytogenic complete remission (CRc).
[a] 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. ANC ≥1.0 × 10^9/L (1000/µL) per the European LeukemiaNet guidelines.

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

[c] A repeat marrow should be performed to confirm relapse with 2 consecutive assessments separated by at least a month. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a subject who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis.

CRh is defined as a CR with partial recovery of peripheral blood counts (< 5% bone marrow blasts, ANC >0.5 × 10^9/L [500/µL], and platelets >50 × 10^9/L [50,000/µL]). Because CRh is not part of modified IWG criteria, it will be derived by the Sponsor.

Table 11: Criteria for Stable Disease and Disease Progression for Acute Myeloid Leukemia

Category	Response criteria
Stable disease	Absence of CR, CRi (including CRp), PR, or MLFS and not meeting the criteria for a PD (disease progression)
Disease progression (defined only for subjects who have not previously attained CR, CRi, CRp, or MLFS)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • > 50% increase in bone marrow blast count over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline); or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 500/µL, and/or platelet count to >50,000/µL non-transfused); • > 50% increase in peripheral blasts (WBC × % blasts) to >25,000/µL in the absence of treatment-related differentiation syndrome; • New extramedullary disease.

Source: (Döhner et al, 2017).
Note: "Non-transfused" refers to no transfusion within 7 days of the lab assessment.
Abbreviations: ANC = absolute neutrophil count; CR = complete remission; CRi = complete remission with incomplete hematologic (neutrophil and/or platelet) recovery; CRp = complete remission with incomplete platelet recovery; MLFS = morphologic leukemia-free state; PLT = platelet; WBC = white blood cell.

10.8.2. Indicators of Clinical Benefit

The clinical activity of the combination of AG-120/placebo and azacitidine will also be assessed using surrogate indicators of clinical benefit, including transfusion frequency (dates of the transfusion and units administered), infection rates, days spent hospitalized, and other efficacy and safety measures that are potentially indicative of clinical benefit. At each study visit, the Investigator will record any changes to these parameters.

10.8.3. Quality of Life

Patient-reported outcome data will be elicited from the subjects in this study. The 2 PRO questionnaires, EORTC QLQ-C30 and the EQ-5D-5L, will be translated as required in the local language. PROs will be assessed via an electronic PRO tool.

The EORTC QLQ-C30 is a validated and reliable self-reported measure of QoL for subjects with cancer who are receiving cancer treatment. The questionnaire consists of 30 questions that are incorporated into 5 functional domains (physical, role, cognitive, emotional, and social); a global

health status/global quality of life; 3 symptom scales (fatigue, pain, and nausea and vomiting); and 6 single items that assess additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and the perceived financial burden of treatment experienced by subjects with cancer (Aaronson et al, 1993; Sprangers et al, 1993). This questionnaire has been used either alone or with specific modules in 40% of more than 100 oncology clinical trials (Lemieux et al, 2011).

The EQ-5D-5L is a generic, preference-based health utility measure with questions that span 5 dimensions of life, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which are used to build a composite of the subject's health status. Applicable to a wide range of health conditions and treatments, EQ-5D-5L provides a simple descriptive profile and a single index value for health status. The use of the EQ-5D-5L in cancer has increased in recent years, and published studies provide evidence to support its validity and reliability (Pickard et al, 2007). The EQ-5D-5L will be utilized in this study for economic modeling.

Both questionnaires have been used in studies of subjects with AML (Amler et al, 2015; Garcia-Manero et al, 2016; Levy et al, 2014; Marques da Silva et al, 2015; Timilshina et al, 2016). For C1D1, both questionnaires should be administered prior to initiating study treatment. For all other applicable study visits, both questionnaires will be administered prior to starting any other study-related assessments.

10.9. Pharmacokinetic and Pharmacodynamic Assessments

Serial blood samples will be drawn before and after dosing of study treatment in order to determine circulating plasma concentrations of AG-120 (Table 7). Blood samples will also be used for the determination of 2-HG concentrations (Table 8).

Blood samples for PK assessments will be drawn pre-dose (within 30 minutes before dose) and at 0.5, 2, and 4 hours post-dose on Day 1 (± 3 days) of Cycles 1 and 2 (Weeks 1 and 5); pre-dose on Days 8 and 15 (± 3 days) of Cycle 1; and pre-dose on Day 1 (± 3 days) of Cycles 3 and beyond (Weeks 9+). For subjects who cross over, only predose PK samples will be collected.

Blood samples for 2-HG assessments will be drawn at pre-dose on Day 1 and Day 15 (± 3 days) of Cycle 1.

10.10. Sample Processing, Storage, and Shipment

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

11. ADVERSE EVENTS

Monitoring of AEs will be conducted throughout the study (once subjects have been consented); SAEs that are assessed as related to study treatment that occur >28 days post-treatment also are to be reported. All AEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Prior to first dose of study treatment, only AEs that are classified as SAEs deemed related to study procedures should be reported.

Adverse Event Reporting Period

Investigators will seek information on AEs at each subject contact, as outlined below. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the AE eCRF.

- After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported (eg, SAEs related to invasive study procedures such as biopsies).
- After initiation of study drug, all AEs and SAEs, regardless of attribution, will be collected. Subjects will be assessed at the Follow-up Visit (4 weeks post-treatment) to determine if any new AEs have occurred. After this period, Investigators should report only SAEs that are considered to be related to study treatment (AG-120/placebo or azacitidine).

11.1. Definition of Adverse Events

11.1.1. Adverse Event

An AE (also referred to as an adverse experience) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, Screening invasive procedures such as biopsies).

An AE can arise from any use of the drug (eg, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Disease progression or death due to disease progression will not be considered an AE (or an SAE) in this study, but will be collected as an outcome or reason for discontinuation, as appropriate. Adverse events (or SAEs) considered as complications of disease progression should be reported. See Section 11.2.7 for more detailed instructions regarding the reporting of disease progression and deaths due to disease progression.

11.1.2. Related Adverse Event

A related AE is any AE for which there is a reasonable possibility that the drug caused the AE.

Assessment of Causality of Adverse Events

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study treatment, indicating "yes" or "no" accordingly (see Table 12). The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, considering especially the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (where applicable)
- Known association of the event with the study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 12: Causal Attribution Guidance

Is the adverse event (AE) suspected to be caused by the study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study treatment; and/or the AE abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	Adverse events will be considered related, unless they fulfill the criteria as specified below: Evidence exists that the AE has an etiology other than the study treatment (eg, pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study treatment (eg, cancer diagnosed 2 days after first dose of study treatment).

11.1.3. Serious Adverse Event

An AE or suspected adverse reaction is considered serious (an SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Fatal (ie, the AE actually causes or leads to death).
- Life-threatening, meaning that the subject was at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form).
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect in a neonate/infant born to a mother or father exposed to study treatment.
- Important medical event as assessed by the Investigator or Sponsor. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe/life-threatening/fatal, or according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

11.2. Procedures for Reporting Adverse Events and Serious Adverse Events

All AEs (serious and non-serious) spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF.

For reports of SAEs, Investigators should record all case details that can be gathered promptly on both the AE and the SAE eCRFs and submit via the Electronic Data Capture (EDC) system. All SAEs are to be reported within 24 hours from the point in time when the Investigator becomes aware of the SAE. All SAEs must be reported whether or not they are considered causally related

to AG-120/placebo. Serious AE forms will be completed and the information collected will include subject number, a narrative description of the event, and an assessment by the Investigator as to the severity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by the Sponsor or Medical Monitor.

In the event that the EDC system is unavailable, a paper SAE and fax coversheet should be completed and faxed/emailed within no more than 24 hours after learning of the event using the fax numbers provided to Investigators in the safety reporting instructions. The information from the SAE report form should be entered into the EDC system as soon as it is available.

If there are serious, unexpected related AEs associated with the use of AG-120/placebo, the Sponsor will notify the appropriate regulatory agency(ies) and all participating Investigators on an expedited basis. The local Institutional Review Board/Independent Ethics Committee (IRB/IEC) will be promptly notified based on local regulations where required by the IRB/IEC of all serious, unexpected related AEs involving risk to human subjects.

Anticipated SAEs

The Sponsor does not plan to report individually, in an expedited manner, specific serious, frequent AEs because these events are anticipated to occur in the study population at some frequency independent of drug exposure.

These SAEs include the following AML-specific manifestations:

- Neutropenia
- Thrombocytopenia
- Anemia
- Viral, bacterial, and fungal infections

All AEs, whether serious or not, will be described in the source documents and on the AE page of the eCRF. All new events, as well as those that worsen in severity or frequency relative to baseline, which occur after subjects have received at least 1 dose of study treatment through 28 days following the last dose of study treatment, must be recorded. Adverse events that are ongoing at the time of treatment discontinuation should be followed through the 4-week (28-day) post-treatment assessment. In addition, SAEs that are assessed by the Investigator as related to study drug must be reported any time the Investigator becomes aware of such an event, even if this occurrence is more than 28 days after the last dose of study treatment.

Information to be reported in the description of each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded).
- The date of onset of the event.
- The date of resolution of the event.
- Whether the event is serious or not.
- Severity of the event (see below for definitions).
- Relationship of the event to study treatment (see Table 12 for definitions).

- Action taken: none; change in the study treatment administration (eg, temporary interruption in dosing); drug treatment required; non-drug treatment required; hospitalization or prolongation of hospitalization required (complete SAE page); diagnostic procedure performed; subject discontinued from study treatment (complete EOT Visit).
- Outcome: subject recovered without sequelae; subject recovered with sequelae; event ongoing; subject died (notify the Medical Monitor within 24 hours, and complete the SAE form).

Severity of all AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the NCI CTCAE version 4.03 (see Appendix 15.9). Adverse events not listed by the CTCAE will be graded as follows:

- Mild: The event is noticeable to the subject but does not interfere with routine activity.
- Moderate: The event interferes with routine activity but responds to symptomatic therapy or rest.
- Severe: The event significantly limits the subject's ability to perform routine activities despite symptomatic therapy.
- Life-threatening: An event in which the subject was at risk of death at the time of the event.
- Fatal: An event that results in the death of the subject.

11.2.1. Diagnosis Versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE term based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

11.2.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

a. If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
b. If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

c. If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
d. If dizziness leads to a fall and subsequent fracture, all 3 events should be reported separately on the eCRF.
e. If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

11.2.3. Adverse Events of Special Interest

An AESI can be serious or non-serious and is an event of special interest to the Sponsor. Ongoing monitoring and rapid communication (within 24 hours) by the Investigator to the Sponsor is required to allow for further characterization and reporting to regulatory authorities.

11.2.3.1. QT Prolongation

Any QT prolongation event assessed as Grade ≥3 (ie, QTcF >500 msec on at least 2 separate ECGs, or QTcF >500 msec or ≥60 msec change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), irrespective of the seriousness, should be reported as an AESI to the Sponsor within 24 hours. See Section 9.9.1 for further details on managing subjects with QT prolongation. Heart-rate corrected QT interval will be calculated using Fridericia's formula ($QTcF=QT/RR^{1/3}$).

11.2.3.2. Leukocytosis

Any event of leukocytosis assessed as Grade ≥3, irrespective of seriousness, should be reported to the Sponsor as an AESI within 24 hours.

See Section 9.13.4.3 for further details on managing subjects with leukocytosis.

11.2.3.3. IDH Differentiation Syndrome

Any event of differentiation syndrome assessed as Grade ≥2, irrespective of seriousness, should be reported to the Sponsor as an AESI within 24 hours. See Section 9.9.2 for further details on managing subjects with differentiation syndrome.

11.2.4. Persistent or Recurrent Adverse Events

A persistent AE is 1 that extends continuously, without resolution, between subject evaluation time points. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens in intensity or grade.

When an AE becomes serious (regardless of changes in grade or severity), the eCRF should be updated to reflect this. As such, a new AE (serious event with onset date for when AE became serious) should be added to the eCRF.

However, the same does not hold true for AEs that change from serious to non-serious events. When an AE does not resolve but is downgraded from a serious to a non-serious event, a new AE is not required to be captured on the eCRF. A resolution date is required to be entered on the

SAE form once an AE changes from a serious to non-serious event since this would result in the SAE resolving.

A recurrent AE is 1 that resolves between subject evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

11.2.5. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

a. Accompanied by clinical symptoms.
b. Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation).
c. Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy.
d. Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (ie, cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range. Where possible, please enter a condition (eg, neutropenia) rather than the lab finding (eg, decreased neutrophils).

11.2.6. Deaths

Deaths occurring during the protocol-specified AE reporting period (see Section 11.2) that are attributed by the Investigator solely to progression of AML should be recorded only on the Treatment and/or Study Discontinuation eCRFs. All other on-treatment deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and reported to the Sponsor within 24 hours.

Death should be considered an outcome and not a distinct event. The underlying medical diagnosis or suspected diagnosis that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only 1 such event should be reported.

The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.

All deaths will be collected. All on-treatment deaths (within the 28 days after last dose of study treatment) should have an associated SAE captured for the event that led to death, except in the event of disease progression (see Section 11.2.7).

During post-treatment survival follow-up, all deaths will continue to be collected, but only those unrelated to disease progression and considered related to study treatment by the Investigator will be captured as SAEs.

11.2.7. Progression of AML

Progression of AML (see Table 11) should not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the subject's underlying AML or does not fit the expected pattern of progression for the disease.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

11.2.8. Pre-existing Medical Conditions

A pre-existing medical condition is 1 that is present at the Screening Visit for this study. Such conditions should be recorded on the Medical History eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

11.2.9. Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 11.1.3), except as outlined below.

The following hospitalization scenarios are *not considered* to be SAEs:

- Hospitalization for respite care.
- Standard procedure for protocol therapy administration; however, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Administration of blood or platelet transfusion as routine treatment of studied indication; however, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling); however, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.

- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF; hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, which has not worsened from baseline.

11.2.10. Overdose or Incorrect Administration

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects.

Any study treatment overdose or incorrect administration of study treatment should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event.

11.3. Pregnancy Reporting

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (eg, spontaneous abortion, which may qualify as an SAE).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or partner of a male subject occurring while the subject is on study treatment, or within 4 weeks (28 days) of the subject's last dose of study treatment, are considered immediately reportable events. If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study treatment should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. In pregnant female subjects, study treatment is to be discontinued immediately and the subject instructed to return any unused study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately using the pregnancy report form. The Investigator must follow up and document the course and outcome of all pregnancies even if the subject was discontinued from the study or if the study has finished. The female subject or partner of a male subject should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy.

All outcomes of pregnancy (from a female subject or the sexual partner of a male subject) must be reported by the Investigator to the Sponsor or Medical Monitor on a Pregnancy Outcome Report form within 4 weeks after he/she has gained knowledge of the delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth,

neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

Females of reproductive potential must have a negative serum pregnancy test prior to the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results. Women of reproductive potential, as well as fertile men with partners who are female with reproductive potential, must agree to use 2 effective forms of contraception (including 1 barrier form) from the time of giving informed consent, during the study, and for 90 days (females and males) following the last dose of study drug. Females of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy or bilateral oophorectomy, or who have not been naturally postmenopausal (ie, who have not menstruated at all) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Males with partners who are female with reproductive potential must agree that they or their partners will use at least 2 effective contraceptive methods (including 1 barrier method) when engaging in reproductive sexual activity throughout the study, and will avoid conceiving for 90 days after the last dose of study treatment.

An effective form of contraception is defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-release systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization. If not using an effective form of contraception, participants must use 2 of the following methods: progestogen-only hormonal contraception; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide. Refer to Section 9.13.2 for potential drug-drug interactions with hormonal contraceptives.

Females of reproductive potential must undergo a urine pregnancy test to be conducted on C1D1 and confirmed negative prior to dosing, and on Day 1 of all subsequent cycles. The test should be conducted pre-dose, and these subjects should undergo a urine pregnancy test at the end of treatment visit.

11.4. Follow-up of Subjects after Adverse Events

11.4.1. Investigator Follow-up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all SAEs considered related to study treatment or trial-related procedures until a final outcome can be reported.

All pregnancies reported during the study should be followed until pregnancy outcome. Pregnancy outcomes should be reported follow reporting instructions provided in Section 11.3.

11.4.2. Sponsor Follow-up

For SAEs, AESIs, and pregnancies, the Sponsor or a designee may follow-up by EDC query, telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

11.4.3. Post-Study Adverse Events

At the EOT visit, the Investigator should instruct each subject to report to the Investigator any subsequent AEs that the subject's personal physician believes could be related to prior study treatment or study procedures.

The Investigator should notify the Sponsor of any death or SAE of concern occurring at any time after a subject has discontinued study participation if the event is believed to be related to prior study treatment or study procedures. The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a subject that participated in this study.

12. STATISTICAL METHODS

12.1. General Statistical Methods

Summaries will be produced for subject disposition, demographic and baseline disease characteristics, efficacy, safety, PK, and PD, as appropriate. Categorical data will be summarized by frequency distributions (number and percentages of subjects). Continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Time-to-event endpoints will be estimated using the Kaplan-Meier (KM) method. Point estimates and 95% CIs will be provided where appropriate, and estimates of the median and other quantiles, as well as individual time points (eg, 3-, 6-, and 12-month rates), will be produced.

All data will be provided in by-subject listings.

The study data will be analyzed and reported in the clinical study report (CSR) based on all subjects' data up to the time when 173 EFS events have been reached in the study. Complete details for all analyses will be provided in the statistical analysis plan (SAP).

12.2. Analysis Sets

The following analysis sets will be evaluated and used for presentation of the data:

- Intent-to-Treat (ITT) Analysis Set: All subjects who are randomized. Subjects will be classified according to the randomized treatment arm. The ITT Analysis Set will be the default analysis set for all analyses, unless otherwise specified.
- Safety Analysis Set (SAS): All subjects who received at least 1 dose of the study treatment. Subjects will be classified according to the treatment received. The SAS will be the primary analysis set for all safety analyses, unless otherwise specified.
- Per-Protocol Analysis Set (PPAS): All subjects in the ITT who have no major protocol deviations. Additional efficacy analyses may be performed using the PPAS. Rules for major protocol deviations resulting in exclusion from the PPAS will be specified in the SAP.
- Pharmacokinetic Analysis Set (PAS): All subjects who have at least 1 post-dose blood sample providing evaluable PK data for AG-120.

12.3. Disposition

A tabulation of subject disposition will be presented by treatment arm (AG-120 + azacitidine arm vs placebo + azacitidine arm), including the number randomized, the number treated, the reasons for treatment discontinuation, and the reasons for study withdrawal. Protocol deviations will be listed.

12.4. Baseline Evaluations

Demographic and baseline disease characteristic data will be summarized by treatment arm. Data to be tabulated will include sex, age, race, ethnicity, and disease-specific information.

12.5. Efficacy Analyses

During treatment, response will be evaluated by the Investigator based on modified IWG Response Criteria for AML (see Section 10.8.1) to determine subject status and continuation on study treatment. These response assessments will be used for the analysis of all efficacy endpoints. Because CRh is not part of modified IWG response criteria, it will be derived by the Sponsor.

To control the overall Type 1 error rate at the 1-sided 2.5% level, the fixed sequence testing procedure (Westfall and Krishen, 2001) will be used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints.

These endpoints will be tested in the following order:

- EFS
- CR rate
- OS
- CR + CRh rate
- ORR

No control of the alpha level will be made for the other analyses. No interim analyses for efficacy are planned.

12.5.1. Analyses of the Primary Endpoint

The analysis for the primary endpoint will be performed at the time when 173 EFS events have occurred. Event-free survival is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by Week 24. Subjects who do not achieve CR by Week 24 will be considered to have had an event at Day 1 of randomization. For the remaining CR responders, the event time will be the time of either disease relapse or death, whichever occurs first. Event-free survival will be censored upon initiation of a new anticancer therapy should a new therapy be initiated prior to any EFS event.

Event-free survival will be tested using the log-rank test stratified by the randomization stratification factors (de novo status and geographic region) based on the data in the ITT Analysis Set. The basis for a claim of efficacy will be the statistical significance of EFS in favor of the AG-120 + azacitidine arm when the 1-sided $p \leq 0.025$ (observed EFS HR ≤ 0.742).

The distribution of EFS will be estimated using the KM method. The KM curves and 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% CIs, will be presented for each treatment arm. The KM estimates at individual time points (eg, 3-, 6-, and 12-month rates) will also be presented for each treatment arm. A Cox regression model stratified by randomization stratification factors will also be used to estimate the HR of EFS. However, given that the assumption of proportional hazards is not met based on the EFS definition, the overall HR is less meaningful in this context. As EFS is a composite endpoint, the estimates presented separately by each component are more meaningful: CR rate by 24 weeks and EFS among those who have achieved CR by 24 weeks. For subjects who achieve CR by 24 weeks, the KM curves

of the EFS distribution and 25th, 50th (median), and 75th percentiles (if estimable) along with their 2-sided 95% CIs will be presented for each treatment arm. A Cox regression model stratified by randomization stratification factors will also be used to estimate the HR of EFS for these subjects. In addition, the ratio of restricted mean survival time, which does not rely on proportional hazards assumptions, between the 2 arms will also be presented to summarize the treatment effect.

Sensitivity analyses will be performed to explore the robustness of the primary analysis results and will include an analysis based on the stratified log-rank test following the ITT principle, where the time of relapse or death is determined using the actual date of relapse or death without censoring for missing disease assessments or start of subsequent anticancer therapy. Additional sensitivity analyses for EFS will be prespecified in the SAP and will include:

- Stratified log-rank test using the PPAS
- Unstratified log-rank test using the ITT
- Stratified log-rank test using the ITT, where for subjects who do not achieve CR by Week 24, instead of being considered to have had an EFS event at Day 1 of randomization, the event time will be either 24 weeks or EOT, whichever is earlier.

Subgroup analyses will be performed based on the stratification factors. The analyses will include the presentation of CR rate by 24 weeks and KM estimates of EFS among subjects who achieved CR by 24 weeks, unstratified log-rank tests, and HRs (with associated 95% CIs) from unstratified Cox regression models. Other subgroup analyses for EFS, including analyses by cytogenetic risk, will be specified in the SAP.

12.5.2. Analyses of the Secondary Endpoints

The key secondary efficacy endpoints are CR rate, OS, CR + CRh rate, and ORR. Additional secondary efficacy endpoints include CR + CRi (including CRp) rate, DOCR, DOCRh, DOR, DOCRi, TTCR, TTCRh, TTR, TTCRi, transfusion requirements (platelet and RBC), rates of infection, days hospitalized, other efficacy and safety measures that are potentially indicative of clinical benefit, change from baseline in QoL assessments, and the rates of CR with IDH1 MC.

Sensitivity analyses and subgroup analyses for the secondary efficacy endpoints will be specified in the SAP.

12.5.2.1. Key Secondary Endpoint Analyses

12.5.2.1.1. Complete Remission Rate

Complete remission rate is defined as the proportion of subjects who achieve a CR. A Cochran-Mantel-Haenszel (CMH) test will be used to compare CR rate between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

12.5.2.1.2. Overall Survival

Overall survival is defined as the time from date of randomization to the date of death due to any cause. Kaplan-Meier curves and KM estimates of OS will be presented for each treatment arm,

including estimates of the median and other quantiles, as well as individual time points (eg, 3-, 6-, and 12-month rates). The log-rank test stratified by the randomization factors will be used to compare OS between the 2 treatment arms. The HR of OS with a 95% CI comparing the AG-120 + azacitidine arm with the placebo + azacitidine arm will be estimated from a Cox proportional hazards model stratified by the randomization stratification factors.

12.5.2.1.3. Complete Remission Plus Complete Remission With Partial Hematologic Recovery Rate

The CR + CRh rate is defined as the proportion of subjects who achieved a CR or CRh. CRh is defined as a CR with partial recovery of peripheral blood counts (< 5% bone marrow blasts, ANC >0.5 × 10^9/L [500/μL], and platelets >50 × 10^9/L [50,000/μL]). Because CRh is not part of modified IWG criteria, it will be derived by the Sponsor. A CMH test will be used to compare the CR + CRh rate between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

12.5.2.1.4. Objective Response Rate

Objective response rate is defined as the rate of CR, CRi (including CRp), PR, and MLFS. The best response is calculated using the following hierarchy: 1) CR; 2) CRi (including CRp); 3) PR; and 4) MLFS. A summary of best response by treatment arm will be produced. A CMH test will be used to compare ORR between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

12.5.2.2. Additional Secondary Endpoint Analyses

12.5.2.2.1. Complete Remission and CRi (Including CRp) Rate

The CR + CRi (including CRp) rate is defined as the proportion of subjects who achieved a CR or CRi (including CRp). A CMH test will be used to compare the CR + CRi (including CRp) rate between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

12.5.2.2.2. DOCR, DOCRh, DOR, and DOCRi

Among subjects who achieved CR, DOCR will be calculated as the date of the first occurrence of CR to the date of first documented disease relapse, or death.

Among subjects who achieved CR or CRh, DOCRh will be calculated as the date of the first occurrence of CR or CRh to the date of first documented disease relapse or death.

Among subjects who achieved CR, CRi (including CRp), PR, and MLFS, DOR will be calculated as the date of the first response to the date of first documented disease relapse, disease progression, or death.

Among subjects who achieved CR or CRi (including CRp), DOCRi will be calculated as the date of the first occurrence of CR or CRi (including CRp) to the date of the first documented relapse or death.

Kaplan-Meier methods will be used to estimate DOCR, DOCRh, DOR, and DOCRi; subjects without relapse, disease progression, or death, as appropriate, at the time of analysis will be censored at the last response assessment date. Kaplan-Meier estimates of DOCR, DOCRh, DOR, and DOCRi will be presented by treatment arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-, 6-, and 12-month rates).

Subjects will be censored for DOCR, DOCRh, DOR, or DOCRi at the time of the start of subsequent anticancer therapy, should it occur prior to any DOCR, DOCRh, DOR, or DOCRi event, as appropriate. Detailed censoring rules will be included in the SAP. Kaplan-Meier estimates of DOCR, DOCRh, DOR, and DOCRi will be presented by treatment arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-, 6-, and 12-month rates).

12.5.2.2.3. TTCR, TTCRh, TTR, and TTCRi

Among subjects who achieved CR, TTCR will be assessed from the date of randomization to the date of first occurrence of CR.

Among subjects who achieved CR or CRh, TTCRh will be assessed from the date of randomization to the date of first occurrence of CR or CRh.

Among subjects who achieved CR, CRi (including CRp), PR, and MLFS, TTR will be assessed from the date of randomization to the date of the first response.

Among subjects who achieved CR or CRi (including CRp), TTCRi will be assessed from the date of randomization to the date of first occurrence of CR or CRi (including CRp).

Time to CR, TTCRh, TTR, and TTCRi will be summarized by treatment arm. Time to CR, TTCRh, TTR, and TTCRi will be presented by treatment arm using descriptive statistics.

12.5.2.2.4. Additional Clinical Benefit

Transfusion requirements (platelet and RBC; number of units), rates of infection, days spent hospitalized, and other efficacy and safety measures that are potentially indicative of clinical benefit will be summarized by treatment arm using descriptive statistics.

12.5.2.2.5. Quality of Life Assessments

Quality of life, as measured by EORTC QLQ-C30, will be evaluated for subjects with a baseline assessment and at least 1 post-baseline QLQ-C30 assessment that generate a score. For total QLQ-C30, each domain score (eg, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), as well as symptom scales, baseline values, and change from baseline for each time point will be summarized by treatment arm using descriptive statistics. Mixed models will also be applied and the details will be specified in the SAP.

Health economic measures, as assessed by the EQ-5D-5L, will be evaluated for subjects with a baseline assessment and at least 1 post-baseline EQ-5D-5L assessment that generate a score. Scores at baseline and change from baseline scores for each time point will be quantified with descriptive statistics by treatment arm.

12.5.2.2.6. Evaluation of IDH1 Mutation Clearance

Complete remission with IDH1 MC is defined as a response of CR where there is no evidence of the IDH1 mutation by molecular techniques to below the level of detection (0.02%-0.04%) for ≥1 on-treatment time point. A CMH test will be used to compare the rate of CR with IDH1 MC between AG-120 + azacitidine and placebo + azacitidine. A logistic regression model will be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

12.6. Exposure and Safety Analyses

Safety will be evaluated by vital signs, the results of ECOG PS, ECG, and ECHO or MUGA for LVEF as clinically indicated (method per institutional standard of care, with the same method used for an individual subject throughout the study; sites in Germany may only use ECHO), clinical laboratory assessments (hematology, chemistry, and coagulation), and assessment of AEs, AESIs, SAEs, AEs leading to discontinuation or death, and concomitant medication use. All safety data will be listed by subject and summarized by treatment arm.

Clinically significant physical examination findings are captured as AEs will be listed by subject.

Concomitant medications will be listed by subject and will be summarized by treatment arm.

A summary of study drug exposure, including number of doses administered, total dose, duration of treatment, dose intensity, and the proportion of subjects with dose modifications, will be summarized by treatment arm. Reasons for dose modifications will be listed by subject and summarized.

12.6.1. Adverse Events

Summary tables for AEs will include any AE that occurs between the first dose of any study drug and 28 days following the last dose of any study drug. The incidence of AEs (new or worsening from baseline) will be summarized according to (Medical Dictionary for Regulatory Activities [MedDRA]) by system organ class and/or preferred term, severity (based on NCI CTCAE version 4.03 grading as assessed by the Investigator; see Appendix 15.9), seriousness, and relation to study treatment. The following summaries will be produced:

- All AEs
- Treatment-related AEs
- Grade ≥3 AEs
- Grade ≥3 treatment-related AEs
- The most commonly reported AEs (ie, those events reported in ≥10% of all subjects)
- SAEs
- Treatment-related SAEs
- AESIs
- Discontinuations due to AEs
- AEs leading to dose modifications

- On-treatment deaths

By-subject listings will be provided for on-treatment deaths (on-treatment is defined as the period starting from the first dose to 28 days after the last dose), AEs, AESIs, SAEs, and AEs leading to discontinuation of treatment.

12.6.2. Laboratory Abnormalities

For laboratory tests included in the NCI CTCAE version 4.03, laboratory data will be graded accordingly; a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, chemistry, and coagulation studies:

- Descriptive statistics for the actual values and/or change from baseline of clinical laboratory parameters over time.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value (for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/[low and high] classification to compare baseline to the worst on-treatment may be generated).
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above-mentioned tables and listings, graphical displays of key safety parameters, such as scatter plots of actual or change in laboratory tests over time or box plots may be specified in the SAP.

12.6.3. Other Safety Data

Descriptive statistics of ECOG PS over time will be summarized by frequency. Shift tables may be provided for ECOG PS from baseline to worst value of post-baseline assessments.

Additional safety analyses may be performed if deemed necessary.

12.7. Pharmacokinetic Analyses

A population PK approach will be performed to assess typical and individual subject PK parameters of AG-120. Descriptive statistics will be used to summarize AG-120 PK concentrations at different nominal time points across subjects.

12.8. Pharmacodynamic Analyses

Descriptive statistics will be used to summarize 2-HG concentrations at different nominal time points across subjects. The potential relationship between plasma exposure of AG-120 and plasma 2-HG levels will be explored with descriptive and graphical methods as appropriate.

For the subjects who have IDH1 mutation results from both local evaluation and central laboratories, the concordance between the 2 tests will be explored.

[redacted]

12.10. Interim Analyses

There are no interim analyses for efficacy planned for this study.

Safety data will be reviewed regularly by an IDMC to ensure the safety of the combination therapy. These reviews will occur after the first 6, 12, 24, and 36 subjects have completed 1 cycle of therapy or discontinued, whichever should occur first. Thereafter, safety reviews will be conducted approximately every 6 months until the study is unblinded for the analysis of the primary endpoint.

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

No imputation will be performed for missing data elements unless specified otherwise.

When tabulating AE data, partial dates will be imputed. Rules of imputation will be specified in the SAP. All response assessments occurring after documented confirmed relapse/progression maybe be listed and analyzed separately.

12.12. Sample Size Estimation

A total of approximately 200 subjects with previously untreated IDH1m AML will participate in this study.

Assumptions for the placebo + azacitidine arm in this study are based on results from Study AZA-AML-001 in newly diagnosed AML patients who are ineligible for intensive IC receiving AG-120 in combination with azacitidine. Preliminary data from Study AZA-AML-001 were obtained under a data exchange agreement with Celgene. Based on results from a retrospective analysis of these data, the CR rate at 24 weeks is assumed to be 20% for the placebo + azacitidine arm. For subjects who achieve CR by 24 weeks, the median EFS is assumed to be 14.6 months. Assumptions for the AG-120 + azacitidine arm in this study are based on results from Study AG-221-AML-005 in newly diagnosed AML patients who are ineligible for intensive IC receiving AG-120 in combination with azacitidine. The CR rate by 24 weeks is

assumed to be 40%. For subjects who achieve CR by 24 weeks, a target HR of 0.76 for EFS (equivalent to a median EFS among responders of 14.6 months in the placebo + azacitidine arm vs 19.2 months in the AG-120 + azacitidine arm, assuming an exponential distribution) is assumed. Based on simulation results, the average overall HR over 10,000 simulations for the entire population is 0.641. Given that the assumption of proportional hazards is not met based on the EFS definition, the overall HR is less meaningful in this context. Therefore, the overall HR for the entire population was not part of the study design assumptions.

Under these assumptions, a total of 173 EFS events are required to provide 80% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis using a stratified log-rank test. Assuming a recruitment period of approximately 44 months, with an accrual rate of 3 subjects per month during the first 10 months and 5 subjects per month thereafter, along with an assumed 5% overall dropout rate, approximately 200 subjects will be randomized to the 2 treatment arms in a 1:1 ratio. Given the above assumptions, it is estimated that the analysis of the primary endpoint for EFS will occur approximately 52 months after the first subject is randomized.

12.13. Power for Analysis of Key Secondary Endpoints

12.13.1. Power for Analysis of Overall Survival

Overall survival will be compared between the 2 treatment arms, provided the primary endpoint of EFS is statistically significant favoring the AG-120 + azacitidine arm. Based on available data (Dombret et al, 2015), the median OS in the placebo + azacitidine arm is expected to be approximately 10.4 months. A target HR of 0.71 for OS (equivalent to a median OS of 10.4 months in the placebo + azacitidine arm vs 14.6 months in the AG-120 + azacitidine arm, assuming an exponential distribution) is assumed. Based on the 200 subjects planned to be enrolled in this study to detect the primary endpoint of EFS, it is estimated that at the time of the final analysis for EFS, approximately 145 deaths will be observed and this will provide 54% power at a 1-sided overall 2.5% level of significance to reject the null hypotheses (HR=1) using a log-rank test.

12.13.2. Power for Analysis of Complete Remission Rate, Complete Remission Plus Complete Remission with Partial Hematologic Recovery Rate, and Objective Response Rate

Based on a retrospective analysis of Study AZA-AML-001, the response rates in the placebo + azacitidine arm are expected to be approximately 20%, 25%, and 32% for CR rate, CR + CRh rate, and ORR, respectively. It is hypothesized that the AG-120 + azacitidine arm will result in an absolute 20% increase in the CR rate, CR + CRh rate, and ORR. Based on the 200 subjects planned to be enrolled in this study to detect the primary endpoint of EFS, the power for the analysis of each of these endpoints at a 1-sided 2.5% level of significance to reject the null hypotheses (odds ratio=1) using a CMH test are presented in Table 13.

Table 13: Power for Analysis of CR Rate, CR + CRh Rate, and ORR

Endpoints	Number of Subjects	Target Response Rate (Azacitidine vs AG-120 + Azacitidine)	Power
CR rate	200	20% vs 40%	86%
CR + CRh rate	200	25% vs 45%	84%
ORR	200	32% vs 52%	81%

Abbreviations: CR = complete remission; CRh = complete remission with partial hematologic recovery; ORR = objective response rate; vs = versus.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Good Clinical Practice

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

13.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Appendix 15.10).

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

13.3. Subject Information and Informed Consent

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

After the study has been fully explained, written informed consent will be obtained from the subject prior to study participation.

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

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

13.4. Subject Confidentiality

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

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

13.5. Protocol Compliance

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

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

13.6. Data Management

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

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

13.7. Source Document/Electronic Case Report Form Completion

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

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

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

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

The Investigator will retain all completed source documents.

13.8. Direct Access to Source Data

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

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

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

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

13.9. Record Retention

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

13.10. Liability and Insurance

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

13.11. Publication of Study Findings and Use of Information

All information regarding AG-120 supplied by the Sponsor or designee to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the

development of AG-120 and a companion diagnostic device and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

14. LIST OF REFERENCES

Aaronson N, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.

Amler S, Sauerland MC, Deiters C, Büchner T, Schumacher A. Factors influencing life satisfaction in acute myeloid leukemia survivors following allogeneic stem cell transplantation: a cross-sectional study. *Health Qual Life Outcomes.* 2015;13(1):28.

Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood.* 2006;107(9):3481-3485.

Buchner T, Berdel WE, Haferlach C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol.* 2009;27(1):61-69.

Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer.* 2007;109(6):1114-1124.

Burnett AK, Russell NH, Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. *J Clin Oncol.* 2012;30(32):3924-3931.

Burnett AK, Russell NH, Hunter AE, et al. Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival. *Blood.* 2013;122(8):1384-1394.

Chen Y, Liu L, Laille E, Kumar G, Surapaneni S. In vitro assessment of cytochrome P450 inhibition and induction potential of azacitidine. *Cancer Chemother Pharmacol.* 2010;65(5):995-1000.

Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol.* 2003;21(24):4642-4649.

Chowdhury R, Yeoh KK, Tian YM, et al. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. *EMBO Rep.* 2011;12(5):463-469.

Dang L, Jin S, Su SM. IDH mutations in glioma and acute myeloid leukemia. *Trends Mol Med.* 2010;16(9):387-397.

Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature.* 2009;462(7274):739-744.

Deschler B, de Witte T, Mertelsmann R, Lubbert M. Treatment decision-making for older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia: problems and approaches. *Haematologica.* 2006;91(11):1513-1522.

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424-447.

Dombret H, Raffoux E, Gardin C. Acute myeloid leukemia in the elderly. *Semin Oncol.* 2008;35(4):430-438.

Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood.* 2015;126(3):291-299.

Estey E, Othus M, Lee SJ, Appelbaum FR, Gale RP. New drug approvals in acute myeloid leukemia: what's the best end point? *Leukemia.* 2016;30(3):521-525.

Fenaux P, Ades L. Review of azacitidine trials in Intermediate-2-and High-risk myelodysplastic syndromes. *Leuk Res.* 2009;33 Suppl 2:S7-11.

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol.* 2010;28(4):562-569.

Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell.* 2010;18(6):553-567.

Garcia-Manero G, Almeida A, Giagounidis A, et al. Design and rationale of the QUAZAR Lower-Risk MDS (AZA-MDS-003) trial: a randomized phase 3 study of CC-486 (oral azacitidine) plus best supportive care vs placebo plus best supportive care in patients with IPSS lower-risk myelodysplastic syndromes and poor prognosis due to red blood cell transfusion-dependent anemia and thrombocytopenia. *BMC Hematol.* 2016;16:12.

Goldberg SL, Hsu JW, Orr AR, et al. 5-Azacitidine therapy in elderly patients with acute myelogenous leukemia yields similar survival compared to 3+7 induction chemotherapy with less transfusional support, bacteremias, and hospital days [ASH abstract]. *Blood.* 2006;108(11):4569.

Kantarjian H, Ravandi F, O'Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood.* 2010;116(22):4422-4429.

Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive

care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol.* 2012;30(21):2670-2677.

Kernytsky A, Wang F, Hansen E, et al. IDH2 mutation-induced histone and DNA hypermethylation is progressively reversed by small-molecule inhibition. *Blood.* 2015;125(2):296-303.

Klepin HD. Elderly acute myeloid leukemia: assessing risk. *Curr Hematol Malig Rep.* 2015;10(2):118-125.

Lee SH, Erber WN, Porwit A, Tomonaga M, Peterson LC, Hematology ICfSI. ICSH guidelines for the standardization of bone marrow specimens and reports. *Int J Lab Hematol.* 2008;30(5):349-364.

Lemieux J, Goodwin PJ, Bordeleau LJ, Lauzier S, Theberge V. Quality-of-life measurement in randomized clinical trials in breast cancer: an updated systematic review (2001-2009). *J Natl Cancer Inst.* 2011;103(3):178-231.

Levy AR, Zou D, Risebrough N, Buckstein R, Kim T, Brereton N. Cost-effectiveness in Canada of azacitidine for the treatment of higher-risk myelodysplastic syndromes. *Curr Oncol.* 2014;21(1):e29-40.

Linda H, von Heijne A. A case of posterior reversible encephalopathy syndrome associated with Gilenya® (fingolimod) treatment for multiple sclerosis. *Front Neurol.* 2015;6:39.

Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. *J Clin Oncol.* 2010;28(14):2348-2355.

Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med.* 2009;361(11):1058-1066.

Marques da Silva P, Haag U, Guest JF, Brazier JE, Soro M. Health-related quality of life impact of a triple combination of olmesartan medoxomil, amlodipine besylate and hydrochlorotiazide in subjects with hypertension. *Health Qual Life Outcomes.* 2015;13:24.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Acute Myeloid Leukemia (Version 1.2017). National Comprehensive Cancer Network; 24 February 2017.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Acute Myeloid Leukemia (Version 2.2018). National Comprehensive Cancer Network; August 2018.

National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program. Cancer statistics factsheets: acute myeloid leukemia. National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program website. https://seer.cancer.gov/statfacts/html/amyl.html. Accessed 24 March 2015.

Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica.* 2012;97(12):1916-1924.

Othus M, van Putten W, Lowenberg B, et al. Relationhip between event-free survival and overall survival in acute myeloid leukemia: A report from SWOG, HOVN/SAKK, and MRC/NCRI. *Haematologica.* 2016.

Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes.* 2007;5:70.

Pleyer L, Burgstaller S, Stauder R, et al. Azacitidine in patients with relapsed/refractory acute myeloid leukemia: retrospective analysis of the Austrian Azacitidine Registry. *Blood.* 2014;124(21):943-943.

Pleyer L, Stauder R, Burgstaller S, et al. Azacitidine in patients with WHO-defined AML - results of 155 patients from the Austrian Azacitidine Registry of the AGMT-Study Group. *J Hematol Oncol.* 2013;6:32.

RARECARE. Surveillance of rare cancers in Europe: cholangiocarcinoma. RARECARE website. http://www.rarecare.eu/. Accessed 2016.

Rizzo JD, Brouwers M, Hurley P, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood.* 2010;116(20):4045-4059.

Rudek MA, Zhao M, He P, et al. Pharmacokinetics of 5-azacitidine administered with phenylbutyrate in patients with refractory solid tumors or hematologic malignancies. *J Clin Oncol.* 2005;23(17):3906-3911.

Sievers EL, Larson RA, Stadtmauer EA, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol.* 2001;19(13):3244-3254.

Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol.* 2006;24(24):3895-3903.

Sperr WR, Piribauer M, Wimazal F, et al. A novel effective and safe consolidation for patients over 60 years with acute myeloid leukemia: intermediate dose cytarabine (2 x 1 g/m2 on days 1, 3, and 5). *Clin Cancer Res.* 2004;10(12 Pt 1):3965-3971.

Sprangers MA, Cull A, Bjordal K, Groenvold M, Aaronson NK. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC Study Group on Quality of Life. *Qual Life Res.* 1993;2(4):287-295.

Thepot S, Itzykson R, Seegers V, et al. Azacitidine in untreated acute myeloid leukemia: a report on 149 patients. *Am J Hematol.* 2014;89(4):410-416.

Timilshina N, Breunis H, Tomlinson G, Brandwein J, Alibhai SM. Do quality of life, physical function, or the Wheatley index at diagnosis predict 1-year mortality with intensive chemotherapy in older acute myeloid leukemia patients? *Leuk Res.* 2016;47:142-148.

Tsai HC, Li H, Van Neste L, et al. Transient low doses of DNA-demethylating agents exert durable antitumor effects on hematological and epithelial tumor cells. *Cancer Cell.* 2012;21(3):430-446.

Tsukada Y, Fang J, Erdjument-Bromage H, et al. Histone demethylation by a family of JmjC domain-containing proteins. *Nature.* 2006;439(7078):811-816.

Turcan S, Rohle D, Goenka A, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature.* 2012;483(7390):479-483.

Vidaza. Package Insert. In. Summit, NJ: Celgene Corporation; 2015.

Visser O, Trama A, Maynadie M, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. *Eur J Cancer.* 2012;48(17):3257-3266.

Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell.* 2010;17(3):225-234.

Westfall PH, Krishen A. Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. *J Stat Plan Inference.* 2001;99:25-40.

Yamane K, Toumazou C, Tsukada Y, et al. JHDM2A, a JmjC-containing H3K9 demethylase, facilitates transcription activation by androgen receptor. *Cell.* 2006;125(3):483-495.

Yen KE, Bittinger MA, Su SM, Fantin VR. Cancer-associated IDH mutations: biomarker and therapeutic opportunities. *Oncogene.* 2010;29(49):6409-6417.

15. APPENDICES

15.1. Representative Examples of Low-Fat or High-Fat, High-Calorie Meals

Representative low-fat breakfasts:

a. 2 slices of white bread toast, 1 tablespoon light fat margarine, 1 tablespoon of jelly, and 8 ounces of skim milk (319 calories and 8.2 grams of fat).
b. 1 cup of cereal, 1 slice of toast with jam, 8 ounces of skim milk, and 1 cup of decaffeinated coffee or tea (520 calories and 2 grams of fat).

A representative high-fat breakfast consists of the following, and may be adapted to the local regional preference: 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk. This representative high-fat breakfast contains approximately 1000 calories and 58 grams of fat.

15.2. New York Heart Association Classification

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

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

15.3. Preparation and Administration of Azacitidine

15.3.1. Subcutaneous Administration of Azacitidine

Reconstitution: Azacitidine degrades rapidly at room temperature following reconstitution; therefore, the azacitidine suspension should be prepared immediately before use or should be refrigerated immediately after reconstitution.

Azacitidine must be reconstituted to form a uniform suspension prior to administration. Aseptically add 4 mL of sterilized water for injection slowly into the vial. Vigorously shake or roll the vial until a uniform, cloudy suspension is achieved. The resulting azacitidine concentration will be 25 mg/mL. Do not filter the suspension after reconstitution as this could remove the active substance.

If a dose in excess of 100 mg (4 mL) is required, repeat the above step for preparation of the suspension. Doses greater than 4 mL should be equally divided into 2 syringes and injected into 2 separate sites. For example a dose of 150 mg (final suspension volume =6 mL) should be

equally divided into 2 syringes with 3 mL suspension in each. All syringes should be prepared prior to starting administration.

Azacitidine is supplied in single-use vials that **cannot** be used more than once.

Subcutaneous Administration: To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved.

For SC dosing, rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least 1 inch (2.5 cm) from the previous site and never into areas where the site is tender, bruised, red, or hard. Subcutaneous doses greater than 100 mg (4 mL) should be divided equally into 2 syringes and injected into 2 separate sites.

Suspension Stability: Azacitidine reconstituted for SC administration should be stored as directed on the label.

15.3.2. Intravenous Administration of Azacitidine

Reconstitution: Reconstitute the appropriate number of vials to achieve the desired dose. Reconstitute each vial with 10 mL of sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

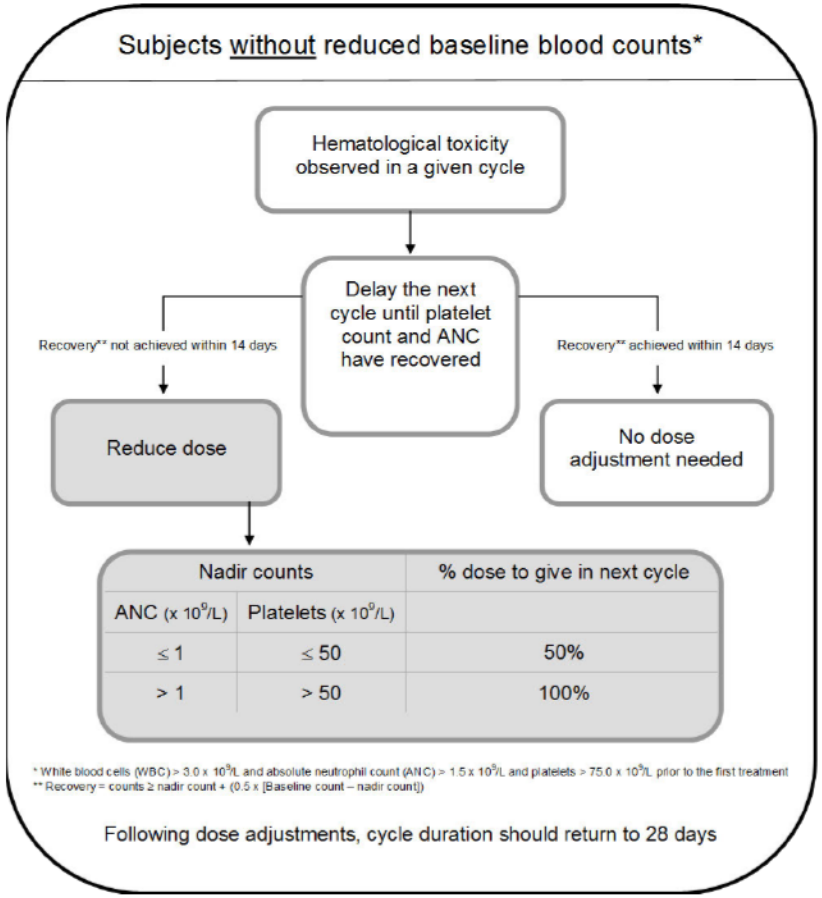
Withdraw the required amount of azacitidine solution to deliver the desired dose and inject into a 50 to 100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

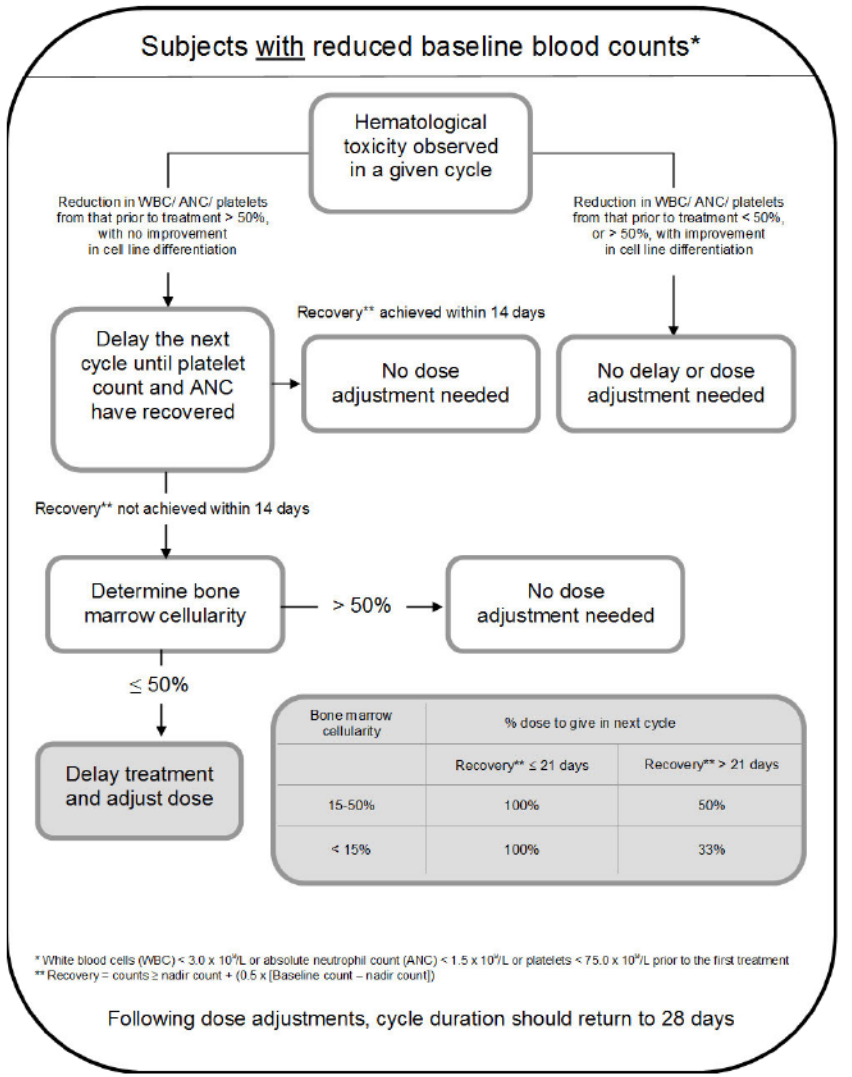
Intravenous Solution Incompatibility: This medicinal product must not be mixed with other medicinal products. Azacitidine is incompatible with dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of azacitidine and should therefore be avoided.

Intravenous Administration: Administer the total dose over a period of 10 to 40 minutes. The administration must be completed within 45 minutes of reconstitution.

Solution Stability: Azacitidine reconstituted for IV administration should be stored as directed on the label.

15.4. Azacitidine Dose Modifications due to Hematologic Toxicity





15.5. Medications Known to Prolong the QT Interval

Amiodarone	Dolasetron	Haloperidol	Ondansetron	Terfenadine
Astemizole	Domperidone	Ibutilide	Palonosetron	Thioridazine
Azithromycin	Droperidol	Itraconazole	Pentamidine	Voriconazole
Bepridil	Erythromycin	Ketoconazole	Pimozide	
Chloroquine	Escitalopram	Levofloxacin	Posaconazole	
Chlorpromazine	Flecainide	Levomethadyl	Probucol	
Ciprofloxacin	Gatifloxacin	Mesoridazine	Procainamide	
Citalopram	Gemifloxacin	Methadone	Quinidine	
Clarithromycin	Granisetron	Moxifloxacin	Sevoflurane	
Disopyramide	Grepafloxacin	Norfloxacin	Sotalol	
Dofetilide	Halofantrine	Ofloxacin	Sparfloxacin	

Note that this is not an exhaustive list. For an updated list, see the following link:
https://crediblemeds.org/healthcare-providers/

15.6. Prohibited Concomitant Medications

Prohibited medications and certain foods are not allowed in this study (Screening Period through End of Treatment) while subjects are receiving study drug.	
Strong CYP3A Inducers	**CYP3A Substrates With a Narrow Therapeutic Index**
Avasimibe, carbamazepine, phenytoin, rifampin, rifabutin, St. John's wort	Alfentanil, astemizole(1), cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, everolimus, sirolimus, tacrolimus, terfenadine(1)

Abbreviations: CYP = cytochrome P450.
Note that this is not an exhaustive list. For an updated list, see the following link:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).
[1] Withdrawn from the United States market because of safety reasons.

15.7. Moderate and Strong CYP3A4 Inhibitors

Moderate CYP3A4 Inhibitors
Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
Strong CYP3A4 Inhibitors
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole
Ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole
Ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

Note: Based on FDA guidelines; Investigators should follow local institutional guidelines, where appropriate.

15.8. Eastern Cooperative Oncology Group Performance Status Scoring

Grade	Symptomatology
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

15.9. National Cancer Institute Common Terminology Criteria for Adverse Events

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

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

15.10. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI:

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, and the 41st WMA General Assembly, Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added); 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added); and 59th WMA General Assembly, Seoul, October 2008, 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the subject's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being, and rights of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development, and effects of diseases and improve preventive, diagnostic, and therapeutic interventions (methods, procedures, and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on subjects or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their subjects in research only to the extent that this is justified by its potential preventive, diagnostic, or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the subjects who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

<u>Risks, Burdens and Benefits</u>

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed, and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices, or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor, and any other undue influence, and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any

serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious subjects, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the subject which aspects of their care are related to the research. The refusal of a subject to participate in a study or the subject's decision to withdraw from the study must never adversely affect the subject-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage, and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

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

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the subjects who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a

duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations, and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

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

15.11. Protocol Amendment History

Changes that had a major impact on the conduct of the study are summarized below.

Amendment 1, Version 2.0 (07 February 2017) Global	• Reduced survival follow-up assessments from every 4 to every 8 weeks. • Revised PK and PD sampling time points. Subjects in the optional safety run-in will not undergo additional PK assessments. Sparse PK blood sampling will not be conducted. Samples for PD will be collected predose only on specified days. • Clarified that prior treatment with hydroxyurea is not exclusionary. • Revised number of azacitidine treatment days, representing at least 75% of the planned azacitidine dose, from 5 to 6. • Clarified the decision to initiate the randomized portion of the trial will be made after 30% of subjects experienced a DLT within the DLT evaluation window of one study treatment cycle. • Removed ambiguous wording around holding and reducing study treatment doses for AE management. • Clarified that weight and body surface area (BSA) assessments must be conducted predose on Day 1 of each cycle. • Added a definition for a limited physical examination. • Revised study treatment discontinuation requirements to indicate that study treatment cannot continue for subjects with progressive disease. • Clarified that performance of the EFS comparison depends solely on statistical significance for the OS endpoint; statistical significance for the key secondary endpoints of CR rate and CR + CRh rate is not required. • Revised instructions on subcutaneous administration and added instructions for intravenous administration of azacitidine consistent with the azacitidine IB.
Amendment 2, Version 3.0 (24 March 2017) Global	• Removed the inclusion of adult individuals who lack the capacity to consent for themselves from the eligibility criteria. • Clarified that azacitidine (Vidaza®) will be supplied as commercial product for investigational use in Brazil. • [redacted] • [redacted] • Specified that the assay to be used to determine the presence of an IDH1 mutation is an investigational PCR assay, Abbott RealTime IDH1.
Amendment 3, Version 4.0 (14 April 2017) Global	• Removed the optional safety run-in portion of the study based on preliminary safety results for the combination of AG-120 and azacitidine in Study AG221-AML-005.

	• Revised the section on unblinding to clarify that the responsibility for breaking the treatment code in emergency situations resides solely with the Investigator and that rapid unblinding is possible when necessary. • Replaced "treatment failure" with "failure to achieve CR or CR with CRi (including CRp) at 24 weeks" for clarity. • Added secondary objectives of rate, duration, and time to CR + CRi (including CRp) to align with the revised definition of EFS, with corresponding endpoints and analyses. • Adjusted the timing of response assessments Week 9 and every eighth week thereafter (Weeks 17, 25, etc) to ensure response assessment after 24 weeks (6 months) of treatment. Quality of life assessments were aligned with response assessments from Week 9 onward. • Clarified the conditions under which subjects may continue to receive AG-120/placebo after discontinuing azacitidine to mitigate the potential for subjects without CR or CRi (including CRp) to continue on single-agent placebo. Subjects may continue to receive AG-120/placebo following discontinuation of azacitidine, provided they are in CR or CRi (including CRp) and need to discontinue azacitidine due to protocol-specified azacitidine-related toxicity (eg, delayed bone marrow recovery). • In response to FDA feedback, removed the attainment of a > 30% reduction in bone marrow blast count percentage as a potential indicator for continued treatment in subjects with a response less than CR or CRi (including CRp) at 24 weeks or beyond. • For consistency with the AG-120 IB, Version 5.0, added that systemic administration of a moderate or strong CYP3A4 inhibitor requires careful QTcF monitoring and that subjects should be routinely monitored for rash. • Removed abstinence as an acceptable form of contraception.
Amendment 4, Version 5.0 (31 October 2017) Global	• Allowed randomization based on local IDH1 mutation testing (central testing is still required however, and blood and bone marrow samples must be received centrally prior to randomization). • Clarified permitted prerandomization therapies for disease stabilization. • Added an exclusion criterion for subjects taking medications that prolong the QT interval, with certain exceptions. • [redacted] • Changed disease assessment schedule including: frequency of bone marrow aspirate collection, submission of bone marrow aspirate, and peripheral blood samples [redacted]. • Added an ECG on Day 1 of each treatment cycle. • Added pregnancy testing for females of reproductive age on Day 1 of each cycle and at the end of treatment.
Amendment 4, Version 5.1 (04 December 2017) Japan	• Updated Japan-specific subject enrollment and safety monitoring. • Added a requirement for sequential enrollment of Japanese subjects until at least 3 subjects have been treated with the combination of AG-120 +

	azacitidine and the combination has been determined to be tolerable in Japanese subjects. • Japanese subjects assigned to the initial safety evaluation cohorts will be hospitalized during the azacitidine treatment period of the first cycle of treatment. • If AEs experienced by Japanese subjects enrolled in the safety evaluation cohorts meet the criteria of a DLT, subsequent enrollment of Japanese subjects will stop and the IDMC will be consulted without delay to review unblinded data and evaluate if it is safe to continue enrolling Japanese subjects. • Added a separate review of safety data by the IDMC for subjects enrolled in Japan.
Amendment 4, Version 5.2 (23 April 2018) Japan	• Aligned the protocol with PMDA requirements. • Prophylactic treatment with granulocyte colony-stimulating factor before initiating treatment with study drug was prohibited because the prophylactic treatment may mask DLTs. Neutropenia treated with granulocyte colony-stimulating factor during the DLT evaluation window will be considered a DLT. • If a subject missed more than 20% of doses of study drug during the DLT evaluation window (2 days of azacitidine or 6 days of AG-120) due to an AE, the AE will be considered a DLT. • Revised inclusion criterion #8 to indicate that in countries where the age of consent is greater than 18 years, for subjects under the age of consent, both the subject and his/her guardian or legal representative must be willing to sign an ICF. • Revised inclusion criterion #10 to indicate that female subjects with amenorrhea due to medication must follow the guidelines for females of reproductive potential, and that the 2 effective forms of contraception must be approved by a local regulatory authority. • Revised exclusion criterion #7 to exclude subjects who interrupt breastfeeding. • Added hepatitis B, hepatitis C, and HIV testing as a Screening assessment, and for seropositive subjects with viral immunity but no evidence of active disease at Screening, viral reactivation will be monitored at Screening and on Day 1 of each cycle.
Amendment 4, Version 5.3 (11 January 2019) France	• Added language to advise Investigators to suspend treatment with AG-120/placebo if a subject is suspected of having PML. • Added a section for "Other Potential Risks" associated with AG-120 including leukoencephalopathy, sensorimotor neuropathy/polyneuropathy, and tumour lysis syndrome.
Amendment 4, Version 5.4 (30 May 2019) Germany	• Updated the potential risks for AG-120 to align with the current edition of the IB (Version 8.0, dated 07 March 2019) and per Health Authority request. • Added an exclusion criterion for subjects with a known medical history of PML.

	• Added the potential risks and management guidelines associated with AG-120, including leukoencephalopathy, sensorimotor neuropathy/polyneuropathy, and tumour lysis syndrome. • Updated the potential drug-drug interactions between AG-120 and azacitidine. • Updated the concomitant medications requiring careful monitoring to include those that are extensively metabolized by CYP2C9 and hormonal contraceptives. • Removed the exclusion criterion for subjects taking P-gp transporter-sensitive substrate medications. • With the exception of the abovementioned changes to the exclusion criteria, this information was provided in the Germany-specific protocol addendum (dated 10 August 2018).
Amendment 5, Version 6.0 (09 January 2020) Global and Amendment 5, Version 6.1 (09 January 2020) Japan	• Changed the primary endpoint from OS to EFS and added OS to the key secondary endpoints, and updated the corresponding statistical analyses. • Updated the additional secondary endpoint evaluating IDH1 mutation clearance (MC) and the corresponding statistical analyses. • Updated the inclusion criterion to more narrowly define a population of patients who are ineligible for intensive IC, and aligned the associated liver and renal function criteria. • For consistency with the current edition of the AG-120 IB, removed the criterion excluding subjects taking P-gp transporter sensitive substrate medications; added a criterion excluding subjects with a medical history of PML as PML is a potential risk of treatment with AG-120; and revised information on drug-drug interactions. • Removed the interim analyses for efficacy. • Reduced the number of subjects who will participate in this study from 392 to 200 based on updated sample size estimations, and increased the number of study centers and countries.
Amendment 6, Version 7.0 (04 March 2020) Global and Amendment 6, Version 7.1 (04 March 2020) Japan	• Clarified that peripheral blood samples may only be used to assess IDH1 mutation (Inclusion Criterion #3) if bone marrow aspirate is not available to ensure clarity and consistency around the samples for IDH1 mutation testing.
Amendment 7, Version 8.0 (16 December 2020) Global and Amendment 7, Version 8.1 (16 December 2020) Japan	• Added a section describing temporary protocol modifications to ensure subject safety, maintain compliance with GCP, and minimize risks to study integrity during a COVID-19 public health emergency. • Continued efficacy follow-up of subjects in the study for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event.

	• Incorporated a sensitivity analysis for the primary endpoint supporting the continued efficacy follow-up for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event.
Amendment 7, Version 8.2 (26 May 2021) Germany	• Clarified language regarding home health study support. • Removed the language regarding obtaining virtual informed reconsent.
Amendment 8, Version 9.0 (01 July 2021) Global, Amendment 8, Version 9.1 (01 July 2021) Japan, and Amendment 8, Version 9.2 (01 July 2021) Germany	• The management of subjects following study unblinding was added. • Added two paragraphs to provide risk assessments for the use of the COVID-19 vaccine to fulfill Health Authority requirements. • Updated to clarify that AG-120 may be shipped to a subject, but azacitidine may not, based on Health Authority feedback. • Removed personal visits and onsite review to permit flexibility under exceptional circumstances.

PROTOCOL AG120-C-009

AMENDMENT 9, VERSION 10.0, 29 SEPTEMBER 2021

SUMMARY OF CHANGES FROM

AMENDMENT 8, VERSION 9.0, 01 JULY 2021

A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ≥18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation

1. OVERVIEW

The protocol was primarily amended to change the Sponsor for the study.

The substantial changes included in the current amendment are itemized as follows:

- Changed the Sponsor from Agios Pharmaceuticals, Inc. (Agios) to Institut de Recherches Internationales Servier (I.R.I.S.)

The changes in the preceding list are detailed in Section 2; added text is in **bold** font and deleted text is in ~~strikethrough~~ font.

Nonsubstantial changes are listed in Section 3.

Editorial changes for improving clarity and style, formatting changes, and corrections of typographical errors are not detailed in this document.

2. DETAILS OF SUBSTANTIAL CHANGES

Substantial Change and Rationale: Changed the Sponsor from Agios Pharmaceuticals, Inc. (Agios) to Institut de Recherches Internationales Servier (I.R.I.S.).		
Primary Section Affected: Cover page		
Formerly Read	Study Sponsor:	~~Agios Pharmaceuticals, Inc.~~ ~~88 Sidney St~~ ~~Cambridge, MA 02139-4169~~ ~~Phone: 617-649-8600~~ ~~Fax: 617-649-8618~~
	Responsible Medical Officer:	[redacted], MD [redacted] ~~Agios Pharmaceuticals, Inc.~~
Now Reads	Study Sponsor:	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50, rue Carnot** **92284 Suresnes cedex - France**
	Responsible Medical Officer:	[redacted], MD [redacted] **Servier Pharmaceuticals LLC**
	Deputy Head:	**[redacted], MD, PhD** [redacted] [redacted] [redacted] **I.R.I.S.**
Other Sections Affected: Removed references to Agios as the Sponsor throughout and added new signatory from I.R.I.S.		

3. LISTING OF NONSUBSTANTIAL CHANGES

Primary Section(s) Affected	Change with Rationale	Other Sections Affected
Cover page	Replaced the confidentiality statement with the word "Confidential" to reflect the new Sponsor's standard practice.	N/A
Protocol Approval	Revised the format of the protocol approval page to reflect the new Sponsor's standard format.	N/A
Investigator's Agreement	Revised the format of the investigator's agreement page to reflect the new Sponsor's standard format.	N/A
Section 11.2, Procedures for Reporting Adverse Events and Serious Adverse Events	Replaced the contact information for safety reporting with a reference to the safety reporting instructions because this contact information is already provided in these instructions and/or other documents.	N/A
Appendix 15.11, Protocol Amendment History	Added previous protocol amendments to summarize changes that had a major impact on the conduct of the study.	N/A