SYNOPSIS

Name of Sponsor/Company Institut de Recherches Internationales Servier	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product Ivosidenib		
Name of Active Ingredient AG-120		

Title of Study

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

Principal Investigator: [redacted]

Study Centers

A total of 199 sites participated in this study (89 sites of which enrolled subjects): 4 sites in Australia, 2 sites in Austria, 13 sites in Brazil, 3 sites in Canada, 16 sites in China, 3 sites in the Czech Republic, 22 sites in France, 17 sites in Germany, 9 sites in Israel, 9 sites in Italy, 12 sites in Japan, 8 sites in South Korea, 6 sites in Mexico, 3 sites in the Netherlands, 5 sites in Poland, 9 sites in Russia, 23 sites in Spain, 6 sites in Taiwan, 6 sites in the United Kingdom, and 23 sites in the United States.

Publications (reference): None

Studied Period (years)	**Phase of Development**
Date first subject enrolled: 19 March 2018 Date last subject completed: N/A, study is ongoing	3

Objectives

Primary

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

Secondary

Key Secondary Objectives

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

- To assess the impact of treatment on health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and 5-level EuroQol Five Dimensions Questionnaire (EQ 5D 5L).
- To evaluate the Pharmacokinetics (PK) of ivosidenib as administered in combination with azacitidine.
- To evaluate the PK/pharmacodynamic (PD) relationship of ivosidenib and 2-HG in blood samples in comparison with placebo.
- To compare rates of CR with IDH1 mutation clearance (MC) between ivosidenib + azacitidine and placebo + azacitidine.

Exploratory

- To evaluate genetic, epigenetic, and global gene expression profiles in bone marrow and/or peripheral blood samples for identification and characterization of biomarkers that may correlate with clinical outcome.
- To characterize PD by evaluation of morphological effects of ivosidenib in acute myeloid leukemia (AML).

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 ivosidenib + azacitidine vs placebo + azacitidine in adult subjects with previously untreated IDH1m AML and who were considered appropriate candidates for non-intensive therapy.

Following provision of informed consent, all subjects were to undergo Screening procedures within 4 weeks (28 days) prior to randomization to determine IDH1 mutation status and other eligibility criteria.

Subjects eligible for study treatment based on Screening assessments were randomized 1:1 to receive oral ivosidenib or matched placebo, both administered in combination with subcutaneous (SC) or intravenous (IV) azacitidine. Randomization was 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 were to be treated for a minimum of 6 cycles of combination therapy unless they experienced relapse after achieving a CR, CRi (including CRp), or morphologic leukemia-free state (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 was to be administered as follows:

- All subjects were to 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 ivosidenib or placebo once daily (QD) on each day of the 4-week cycle. The same schedule was to be used for each subject throughout the duration of treatment, when possible.
- Subjects were to continue to receive therapy with ivosidenib 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.
  - Disease progression (defined only for subjects who have not previously attained CR, CRi, CRp, or MLFS) was 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 was 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 (> 500/µL, and/or platelet count to >50,000/µL nontransfused); 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 could 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 were to have the extent of their disease assessed by bone marrow aspirate (extent of disease may have been 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 was 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 end of treatment (EOT); during event-free survival (EFS) follow-up on the same schedule; as clinically indicated; and/or any time that disease progression was suspected. The disease assessment schedule was not to 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 was to be evaluated by the Investigator based on modified International Working Group (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. Investigator response assessments were to be used for the analysis of all efficacy endpoints, unless otherwise defined.

All subjects underwent safety assessments throughout the treatment period, to include physical examination, vital signs, Eastern Cooperative Oncology Group performance status (ECOG PS), electrocardiogram (ECG), 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 subject throughout the study; sites in Germany may only use ECHO), clinical laboratory assessments (hematology, chemistry, coagulation), and assessment of AEs, AESIs, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation or death, and concomitant medication use. Toxicity severity was graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) version 4.03.

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

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

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

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

The PK/PD of ivosidenib was evaluated using serial blood sampling for PK and sparse sampling for PD. Blood samples for assessment of ivosidenib plasma concentrations for PK plasma concentrations were collected over a 4-hour period on Cycle 1, Day 1 and Cycle 2, Day 1. Additional PK blood samples were collected pre-dose on Days 8 and 15 of Cycle 1; and pre-dose on Day 1 of Cycle 3 and Day 1 of each treatment cycle thereafter. Blood samples for assessment of 2-HG plasma concentrations for pharmacodynamic analysis were collected at pre-dose on Cycle 1, Day 1 and Cycle 1, Day 15.

Number of Subjects (Planned and Analyzed)

Planned

Approximately 200 subjects (100 per treatment arm) were planned for enrollment in the study.

Analyzed

As of the 18 March 2021 data cutoff, 146 subjects have been randomized. The study is ongoing. The following data sets were analyzed:

- 146 subjects were included in the full analysis set (FAS) (all randomized subjects)
    - 141 (96.6%) subjects were included in the per protocol set (PPS)
    - 77 (52.7%) subjects were included in the biomarker analysis set (BAS)
- 144 subjects were included in the safety analysis set (SAS) (all subjects who received at least 1 dose of study treatment).

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria

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

1. Were ≥18 years of age and met at least 1 of the following criteria defining ineligibility for intensive 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 the upper limit of normal (× upper limit of normal [ULN])
   g. Any other comorbidity that the Investigator judged to be incompatible with intensive IC were required to be reviewed and approved by the Medical Monitor before study enrollment.
2. Had previously untreated AML, defined according to World Health Organization (WHO) criteria. Subjects with extramedullary disease alone (ie, no detectable bone marrow and no detectable peripheral blood AML) were not eligible for the study.
3. Had 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 was not available, with Medical Monitor approval).
   – (Note: Local testing for eligibility and randomization was permitted with Medical Monitor approval; however, results had to 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 was 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. Had an ECOG PS score of 0 to 2 (see Appendix 15.8 of AG120-C-009 protocol, Version 10.0, Appendix 16.1.1).
5. Had 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 had to 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. Had 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. Agreed to undergo serial blood and bone marrow sampling.
8. Were able to understand and willing to sign an informed consent form (ICF).
9. Were 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 had a negative serum pregnancy test prior to the start of study therapy. Female subjects with reproductive potential were defined as sexually mature women who had not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who had 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, were required to 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 were 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 ivosidenib may decrease the concentrations of hormonal contraceptives.

Exclusion Criteria

Subjects who met any of the following criteria were not to be enrolled in the study:

1. Were candidates for intensive IC for their AML.
2. Had received any prior treatment for AML with the exception of nononcolytic treatments to stabilize disease such as hydroxyurea or leukapheresis.
3. Had received a hypomethylating agent for myelodysplastic syndrome (MDS).
4. Subjects who had previously received treatment for an antecedent hematologic disorder, including investigational agents, were not to be randomized until a washout period of at least 5 half-lives of the investigational agent had elapsed since the last dose of that agent.
5. Had received prior treatment with an IDH1 inhibitor.
6. Had a known hypersensitivity to any of the components of ivosidenib, matched placebo, or azacitidine.
7. Were female and pregnant or breastfeeding.
8. Were taking known strong cytochrome P450 (CYP)3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they could be transferred to other medications within ≥5 half-lives prior to dosing (see Appendix 15.6 of AG120-C-009 protocol, Version 10.0, Appendix 16.1.1).
9. Exclusion Criterion #9 was removed in Protocol Amendment 5, Version 6.0.
10. Had an active, uncontrolled, systemic fungal, bacterial, or viral infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
11. Had a prior history of malignancy other than MDS or myeloproliferative disorder, unless the subject had 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 were 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. 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. Had a heart-rate corrected QT interval using Fridericia's method (see Appendix 15.5of AG120-C-009 protocol, Version 10.0, Appendix 16.1.1) (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 could participate in the study.
14. Had a known infection caused by human immunodeficiency virus (HIV) or active hepatitis B virus or hepatitis C virus that cannot be controlled by treatment.
15. Had dysphagia, short-gut syndrome, gastroparesis, or any other condition that limits the ingestion or gastrointestinal absorption of orally administered drugs.
16. Had uncontrolled hypertension (systolic blood pressure [BP] >180 mmHg or diastolic BP >100 mmHg).
17. Had clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid during Screening was only required if there was a clinical suspicion of CNS involvement by leukemia during Screening.
18. Had immediate, life-threatening, severe complications of leukemia, such as uncontrolled bleeding, pneumonia with hypoxia or sepsis, and/or disseminated intravascular coagulation.

19. Had 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. Were taking medications that are known to prolong the QT interval (see Appendix 15.5 of AG120-C-009 protocol, Version 10.0, Appendix 16.1.1) unless they could be transferred to other medications within ≥5 half-lives prior to dosing, or unless the medications could be properly monitored during the study. (If equivalent medication was not available, heart rate corrected QT interval [QTc] were to be closely monitored).
21. Subjects with a known medical history of progressive multifocal leukoencephalopathy (PML).

Investigational Product, Dosage and Mode of Administration, Batch Number

Ivosidenib was supplied as 250 mg strength tablets to be administered orally.

Placebo was supplied as matched tablets to be administered orally.

Ivosidenib (500 mg) or matched placebo was to be administered orally QD (approximately every 24 hours) during Weeks 1 to 4 in continuous 4-week (28-day) cycles.

Subjects were to receive azacitidine 75 mg/m2/day SC or IV for 1 week every 4 weeks until the end of the study, unless they were discontinued from the treatment. Subjects received 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. Site staff administered all doses of azacitidine when given as study drug.

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

Subjects were 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). Dosing interruptions or delays or dose modifications were permitted for managing toxicities and/or treatment response during study treatment.

Duration of Treatment

Subjects were to continue to receive therapy with ivosidenib 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.

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo was supplied as matched tablets to be administered orally on the same schedule as ivosidenib.

Criteria for Evaluation

Efficacy

The efficacy of ivosidenib was evaluated by Investigator-assessed response to treatment based on modified IWG Response Criteria for AML and ELN guidelines. Disease response to treatment was assessed through the evaluation of bone marrow biopsies and/or aspirates, along with complete blood counts and examination of peripheral blood films. The clinical activity of the combination of ivosidenib/placebo and azacitidine was also to 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. Patient-reported outcome data were obtained via EORTC QLQ-C30 (for HRQoL) and EQ-5D-5L (for health economic outcome) measures.

Safety

Monitoring of AEs, including serious AEs (SAEs), and AEs leading to discontinuation; safety laboratory parameters; physical examination findings; vital signs; 12-lead ECGs; LVEF; and ECOG PS.

The severity of AEs was assessed by the NCI CTCAE version 4.03.

Statistical Methods

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

All data were provided in by-subject listings.

The study data were analyzed and reported in the clinical study report (CSR) based on all subjects' data up to the data cutoff date.

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

The key secondary endpoints

- CR rate (CR defined as bone marrow blasts <5% and no Auer rods, absence of extramedullary disease, ANC ≥1.0×109/L [1000/μL], platelet count ≥100×109/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 >0.5×109/L [500/μL], and platelet count is >50×109/L [50,000/μL]; CRh was derived by the Sponsor)
- ORR, defined as the rate of CR, CRi (including CRp), partial remission (PR), and MLFS

Additional secondary endpoints

- CR+CRi (including CRp) rate (CRi [including CRp] was defined as all CR criteria except for residual neutropenia where ANC was <1.0×109/L [1000/μL] or thrombocytopenia where platelet count was <100×109/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 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 or MLFS; and TTCRi, among subjects who achieved CR or CRi (including CRp)
- Vital signs, and 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 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 were potentially indicative of clinical benefit
- Changes from baseline in QoL assessments (EORTC QLC-C30 and EQ-5D-5L)
- Rates of CR with IDH1 MC
- Ivosidenib/placebo and azacitidine drug exposure, including dose modifications and dose intensities
- Ivosidenib and 2-HG concentrations in circulating plasma

Exploratory Endpoints

Evaluation of a variety of established and exploratory biomarkers for morphologic, functional, metabolic, and biologic changes over the course of treatment.

Analysis Populations

Only subjects who signed informed consent and were screened were included in the analysis sets below.

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

- The FAS included all subjects who were randomized. Subjects were classified according to the randomized treatment arm. (Note: this data set was referred to as the Intent-to-Treat Analysis Set in the protocol.)
- The SAS included all subjects who received at least 1 dose of the study treatment. Subjects were classified according to the treatment received, where treatment received was defined as:
  - The randomized treatment if it was received at least once, or
  - The first treatment received if the randomized treatment was never received

- The PPS was a subset of the FAS. Subjects who met any of the following criteria were excluded from the PPS:
  - Did not receive at least 1 dose of the randomized treatment
  - Eligible for IC
  - Did not have an IDH1 mutation as determined by central laboratory testing
  - Had an ECOG PS score >2
  - Had received any prior treatment for AML with the exception of nononcolytic treatments to stabilize disease such as hydroxyurea or leukapheresis
  - Had received any prior hypomethylating agent
  - Had received any prior IDH1 inhibitor
- The BAS was a subset of the FAS and included all subjects who had at least 1 on-treatment biomarker sample providing valid IDH1m variant allele frequency (VAF) data.

Treatment-emergent adverse events (TEAEs) were AEs with a first onset date during the on treatment period or worsening from baseline. All summaries described below were based on TEAEs, if not otherwise specified.

All AEs were listed by subject and AEs with onset outside of the on-treatment period were flagged in the listings. Unless otherwise specified, TEAEs were summarized according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and/or Preferred Term (PT), severity (based on CTCAE v4.03 grading), seriousness, and relation to study treatment in decreasing frequency based on the frequencies observed for the ivosidenib + azacitidine arm.

Changes to the Planned Analyses

In the SAP, it was stated that the CSR would include all data up to the data cutoff date that would be determined on the number of events required for the final analysis of the primary endpoint (EFS) and a minimum follow-up of 24 weeks for all subjects randomized, but this changed due to the IDMC recommendation (see below).

Due to the changes of the study, in addition to the fixed sequence testing procedure pre-specified in the SAP, an individual set of group-sequential boundaries were applied separately to each of the primary and key secondary efficacy endpoints to account for this unplanned analysis and early termination of the study. Specifically, the O'Brien-Fleming alpha spending function (the Lan-DeMets method) was used for each of the primary and key secondary efficacy endpoints. At the time of the analysis, for each of the primary and key secondary endpoints, the p-value calculated based on methodologies pre-specified in the SAP were compared to the p-value boundary calculated from the alpha spending function, respectively. EAST version 6.5 and R version 4.0.5 were used for the calculation. For EFS, CR, OS, CR+CRh, and ORR, the 1-sided p-value boundaries are 0.0046, 0.0087, 0.0017, 0.0087, and 0.0087, respectively.

In addition to disease assessments performed before the start date of the subsequent anticancer therapies, disease assessments performed on the start date of the subsequent anticancer therapies were also considered in the determination of relapse.

As of the data cutoff date, 10 subjects remained on treatment with less than or equal to 24 weeks who had not yet achieved CR. These subjects could not be evaluated for treatment failure and were censored at the date of randomization. These scenarios were not outlined in the SAP.

For each category specified in the subgroup analyses for EFS, treatment arms were also compared for OS using a 2-sided unstratified log-rank test and the unstratified HR and its corresponding 95% CI were computed. The results are depicted in a Forest plot.

Baseline transfusion dependence, post-baseline transfusion independence and conversion from baseline transfusion dependence to post-baseline transfusion independence were summarized by transfusion type (i.e., RBC, platelet, RBC and/or platelet and RBC and platelet) and treatment arm.

No other changes occurred between the final SAP (version 1.0 dated 22 June 2020) and the CSR. Changes from the protocol-specified analysis to the SAP included the following: a) the Intent-to-treat Analysis Set in the protocol was referred to as the FAS in the SAP and b) the estimation of the treatment effect in terms of odds ratio utilized the Mantel-Haenszel estimate of odds ratio (the 95% CI provided directly from the Cochran-Mantel-Haenszel (CMH) option in SAS PROC FREQ) instead of using the logistic regression model.

Summary – Conclusions

IDMC Unplanned Analyses and Recommendation to Discontinue Treatment

On 04 November 2020, the IDMC met to review the safety data as part of their semi-annual monitoring of the study. During the closed meeting session, when unblinded data was reviewed, the IDMC observed that more deaths were occurring in the placebo + azacitidine arm vs. the ivosidenib + azacitidine arm. The IDMC recommended the sponsor continue the study as planned and in closed session requested additional analyses. These analyses were reviewed at an ad-hoc IDMC meeting on 08 December 2020; no significant difference between the treatment arms could be concluded. At the subsequent IDMC meeting held on 12 May 2021, the IDMC met to review the safety data based on the 146 subjects enrolled in the study at the 18 March 2021 data cut date. A greater number of deaths in the placebo + azacitidine arm vs. the ivosidenib + azacitidine arm continued to be observed. This prompted another unblinded analysis for efficacy, which included OS, EFS, and clinical response, and led to the IDMC recommendation to halt recruitment to the study on 12 May 2021. Servier maintained the blind for the critical study team members directly involved with study conduct, while segregating a small unblinded group to address the IDMC recommendation. On 24 May 2021, unblinded Servier team members, in consultation with the Sponsor Agios, obtained FDA input regarding the IDMC recommendation to halt recruitment; on 27 May 2021 Servier instructed investigators to discontinue recruitment to the study. At that time, 148 subjects had been randomized (2 additional from the18 March 2021 data cut date). The database for the study was locked on 15 July 2021. On 30 July 2021, Investigators were informed that the study met its primary endpoint and all key secondary endpoints and they were given instructions on how to unblind the subjects' treatment assignments. Subjects on the placebo + azacitidine arm were given the opportunity to cross over to the ivosidenib + azacitidine arm if additional safety inclusion and exclusion criteria were met. This change in study conduct (i.e. allowance of cross over) was detailed in AG120-C-009 protocol, Version 9.0 dated 01 July 2021 (Appendix 16.1.1). The p-value boundaries for the primary and key secondary efficacy endpoints were adjusted to account for the IDMC's unplanned analyses as described above.

Efficacy Results

The primary efficacy endpoint was met, with a robust improvement in EFS among subjects with previously untreated IDH1 mutation-positive AML treated with the ivosidenib + azacitidine combination therapy versus those treated with the placebo + azacitidine combination (1-sided P=0.0011; HR = 0.33; 95% CI: 0.16-0.69). As EFS is a composite endpoint of CR rate by 24 weeks and EFS among subjects who achieved CR by 24 weeks, the estimates for each component were summarized. CR rate by 24 weeks was 37.5% (95% CI: 26.4- 49.7) in the ivosidenib + azacitidine arm and 10.8% (95% CI: 4.8-20.2) in the placebo + azacitidine arm. Among subjects who achieved CR by 24 weeks, median EFS was NE (95% CI: 14.8- NE months) in the ivosidenib + azacitidine arm and 17.8 months (95% CI:9.3- NE months) in the placebo + azacitidine arm. The durability of the treatment effect was demonstrated in the ivosidenib + azacitidine arm as higher EFS rates at 12, 18, and 24 months. The durability of treatment effect of ivosidenib + azacitidine combination therapy is represented by the EFS rates at 12 and 24 months of 37.4% and 22.2%, respectively, versus 12.2% and NE in the placebo + azacitidine combination (i.e., no subjects in the placebo + azacitidine arm had EFS of ≥ 24 months by the data cutoff date, with the longest EFS being censored).

Additionally, this robust improvement in EFS was consistently observed in the majority of the subgroups of the FAS and the planned sensitivity analyses.

All key secondary efficacy endpoints were met, with CR, OS, CR+CRh and OR rates statistically significantly higher in the ivosidenib + azacitidine arm versus the placebo + azacitidine arm. CR was achieved in 47.2% (95% CI: 35.3-59.3) of the subjects in the ivosidenib + azacitidine arm and 14.9% (95% CI: 7.7-25.0) of the subjects in the placebo + azacitidine arm. Odds ratio was 4.76 (95% CI: 2.15-10.50; 1-sided P<0.0001). The OS was robustly positive with a HR=0.44 (95% CI: 0.27-0.73; 1-sided P = 0.0005) and a median OS of 24.0 months (95% CI: 11.3- 34.1 months) in the ivosidenib + azacitidine arm and 7.9 months (95% CI: 4.1-11.3 months) in the placebo + azacitidine arm. CR + CRh was achieved in 52.8% (95% CI:40.7- 64.7) of the subjects in the ivosidenib + azacitidine arm and 17.6% (95% CI: 9.7-28.2) of the subjects in the placebo + azacitidine arm. Odds ratio was 5.01 (95% CI: 2.32- 10.81; 1-sided P<0.0001). ORR was achieved in 62.5% (95% CI: 50.3- 73.6) of the subjects in the ivosidenib + azacitidine arm and 18.9% (95% CI: 10.7- 29.7) of the subjects in the placebo + azacitidine arm. Odds ratio is 7.15 (95% CI:3.31- 15.44; 1-sided P<0.0001).

The additional secondary efficacy endpoints CR + CRi (including CRp), DOCR, DOCRh, DOR, DOCRi, TTCR, TTCRh, TTR, TTCRi also favored the ivosidenib + azacitidine arm compared to placebo + azacitidine. CR + CRi (including CRp) was achieved 54.2% (95% CI: 42.0-66.0) of the subjects in the ivosidenib + azacitidine arm and

16.2% (95% CI:8.7-26.6) of the subjects in the placebo + azacitidine arm. The median time to first CR was 4.25 months (range, 1.7 to 9.2) in the ivosidenib + azacitidine arm and 3.81 months (range: 1.9 to 8.5) in the placebo + azacitidine arm. The median duration of response was 22.1 months (95% CI: 13.0-NE months) and 9.2 months (95% CI, 6.6 to 14.1 months), respectively. The median time to first response was 2.07 months (range: 1.7 to 7.5 months) in the ivosidenib + azacitidine arm and 3.68 months (range: 1.9 to 9.4 months) in the placebo + azacitidine arm. In addition, CR with IDH1 MC rate is significantly higher in the ivosidenib + azacitidine arm versus the placebo + azacitidine arm for BMMCs (odds ratio is 7.97; 95% CI: 1.60-39.65; nominal 1-sided P=0.0027) and PBMCs (odds ratio is 3.73; 95% CI: 1.08-12.85; nominal 1-sided P=0.0171).

Baseline and on-treatment transfusion rates were similar between the ivosidenib + azacitidine and placebo + azacitidine arms. However, a greater proportion of subjects who were transfusion dependent at baseline experienced transfusion independence in the ivosidenib + azacitidine arm compared to subjects in the placebo + azacitidine arm. On-study hospitalization for adverse event rates were similar for subjects in the ivosidenib + azacitidine arm compared to the placebo + azacitidine arm, while infections were less frequent in the ivosidenib + azacitidine arm.

The efficacy data are further supported by the HRQoL data. Quality of life assessed via the EORTC-QLQ-C30 and EQ-5D-5L questionnaires showed that the clinical benefits in the ivosidenib + azacitidine arm were supported by stabilization and clinically meaningful improvements in multiple HRQoL domains, including Global Health Status and Fatigue.

The totality of efficacy and HRQoL data demonstrate the clinical benefit of the combination of ivosidenib + azacitidine in adults with previously untreated AML with an IDH1 mutation.

Pharmacokinetics/Pharmacodynamics

Ivosidenib was rapidly absorbed following single and multiple QD 500 mg ivosidenib doses when given in combination with azacitidine. Ivosidenib exposures on Cycle 2, Day 1 were higher than those on Cycle 1, Day 1, with low to moderate accumulation. Plasma 2-HG concentrations for all subjects with previously untreated IDH1 mutation-positive AML were elevated at baseline and plasma 2-HG concentrations remained unchanged compared to baseline after multiple doses of placebo + azacitidine on Cycle 1, Day 15. However, in subjects treated with ivosidenib + azacitidine, plasma 2-HG concentrations on Cycle 1, Day 15 decreased from baseline to levels close to those observed in healthy subjects. Mean plasma 2-HG percent inhibition (based on pre-dose) was 80% (>90% based on the median value) following multiple administration of ivosidenib + azacitidine on Cycle 1, Day 15.

Safety Results

Ivosidenib + azacitidine use in subjects with previously untreated AML was tolerated and the safety profile was manageable.

QT prolongation, Differentiation syndrome, and Leukocytosis are known risks of ivosidenib and were to be reported as AESIs in Study AG120-C-009 when assessed as ≥Grade 3 (QT prolongation, Leukocytosis) or ≥Grade 2 (Differentiation syndrome). Any grade events of Electrocardiogram QT prolongation (19.7%), Differentiation syndrome (14.1%), and Leukocytosis (white blood cell count decreased [2.8%] and Leukocytosis [11.3%]) were among the commonly reported TEAEs in ivosidenib + azacitidine-treated subjects; however, the majority of these individual events were low grade and resolved with dose modification. Only 1 subject experienced an AESI which led to ivosidenib discontinuation (Grade 3 ECG QT prolonged). Furthermore, none of the subjects experienced ventricular tachycardia or ventricular arrhythmia. There were no Grade 4 or 5 TEAEs with a PT of Electrocardiogram QT prolonged, Differentiation syndrome, or Leukocytosis reported in any subject.

Bleeding and infections were characterized as treatment-emergent adverse events of interest in this study based on event specific Standardised MedDRA Queries (SMQs). Bleeding events (defined by the Hemorrhages [excluding laboratory abnormalities] broad SMQ) occurred with higher incidence in ivosidenib + azacitidine-treated subjects (40.8%) compared to placebo + azacitidine-treated subjects (28.8%). In the ivosidenib + azacitidine arm, events were primarily low grade and included: Haematoma, Epistaxis, Petechiae, and Contusion. In the majority, dose was not changed and either resolved or was resolving at the time of the data cutoff. No Grade 4 bleeding events were reported. Two fatal events of Haemorrhage intracranial were reported; one subject died at home with no documented evidence of intracranial hemorrhage and the other subject had multiple confounding factors (severe pulmonary infection, low platelet and white blood cells, severe anemia, and renal failure) in the context of the fatal intracranial hemorrhage. The majority of Bleeding TEAEs occurred in the

setting of low platelet counts (Grade 1 [n=4 TEAEs], Grade 2 [n=3 TEAEs], Grade 3 [n=14 TEAEs], and Grade 4 [n =27 TEAEs]) and 7 Hemorrhage TEAEs occurred in the context of Grade 0 platelet, low.

Overall, infections (defined by the Opportunistic infections broad SMQ) occurred more frequently in the placebo + azacitidine arm than in the ivosidenib + azacitidine arm (49.3% versus 28.2%, respectively). Incidence of Grade 3 (14.1% and 16.4%) and Grade 4 (4.2% a4.1%) infections were comparable between the ivosidenib + azacitidine arm versus the placebo + azacitidine arm; however, infections leading to death was higher in the placebo + azacitidine arm (9.6%) than the ivosidenib + azacitidine arm (2.8%). Coronavirus disease 2019 (COVID-19) and Septic shock led to on-study deaths in the ivosidenib + azacitidine arm, each reported in 1 subject and in the placebo + azacitidine arm, infections leading to on-study deaths included Sepsis and Septic shock (2 subject each, respectively), and Bronchopulmonary aspergillosis, COVID-19 pneumonia, and Corynebacterium sepsis (1 subject each). In addition to infections, Febrile neutropenia was reported with higher incidence in the placebo + azacitidine-treated subjects as compared to ivosidenib + azacitidine-treated subjects (25 [34.2%] and 20 [28.2%] subjects, respectively).

Overall, the median duration of exposure in the ivosidenib + azacitidine arm was > 2 times longer than matched placebo + azacitidine. TEAEs were reported by > 98% of subjects in both treatment arms and the SOCs of very common TEAEs (incidence ≥10%) reported were similar in both treatment arms, i.e. Gastrointestinal disorders, Blood and lymphatic system disorders, Infections and infestations, and General disorders and administration site conditions. Treatment differences of ≥5% incidence in PTs (reported at a higher frequency in the ivosidenib + azacitidine arm compared to placebo + azacitidine) were observed for TEAEs of Vomiting, Neutropenia, Thrombocytopenia, Electrocardiogram QT prolonged, Insomnia, Differentiation syndrome, Pain in extremity, Haematoma, Arthralgia, Headache, Leukocytosis, and Leukopenia. Aside from Neutropenia, Thrombocytopenia, Electrocardiogram QT prolonged and Leukopenia that were reported as Grade ≥3 in ≥5% subjects, these TEAEs were predominantly low grade and did not lead to more treatment discontinuations of the ivosidenib + azacitidine combination.

Common treatment-related TEAEs (in ≥5% subjects) considered by the Investigator as related to ivosidenib treatment were Electrocardiogram QT prolonged, Leukocytosis, and Differentiation syndrome; these TEAEs were also reported as related to placebo but at lower frequencies. The only Grade ≥3 TEAE considered by the Investigator as related to ivosidenib treatment and reported with a ≥5% difference to placebo-related TEAEs was Electrocardiogram QT prolonged (7.0% versus 1.4% subjects).

Serious TEAEs were reported in 69.0% subjects in the ivosidenib + azacitidine arm and 82.2% subjects in the placebo + azacitidine arm. Serious TEAEs reported with a ≥2% higher incidence in the ivosidenib + azacitidine arm as compared to placebo + azacitidine were COVID-19, Differentiation syndrome, Pulmonary embolism, Pleural effusion, and Haemorrhage intracranial. Conversely, serious TEAEs reported with ≥2% lower incidence in the ivosidenib + azacitidine arm compared to placebo + azacitidine arm were Pneumonia, Febrile neutropenia, Anal abscess, Diverticulosis, Parotitis, General physical health deterioration, Epistaxis, and Diarrhoea. Overall, ivosidenib + azacitidine-related serious TEAEs were more common than placebo + azacitidine-related serious TEAEs (22.5% versus 12.3%); however there were no clinically relevant differences in incidence between ivosidenib-related and placebo-related serious TEAEs at the PT level.

Based on laboratory assessments, 1 subject (1.4%) in the ivosidenib + azacitidine arm met criteria for potential Hy's Law (concurrent AST >3xULN, total bilirubin >2xULN); however, this subject had multiple contributing factors and confounders that could explain these liver elevations. The subject received only 4 days of ivosidenib + azacitidine treatment when the liver enzymes began to increase. The subject had rapidly progressing multiple organ dysfunction syndrome in the setting of sepsis requiring treatment with vasopressors (implying hypotension and hypoperfusion) as well as the use of multiple concomitant medications which could independently or in combination have an adverse effect on the liver. While there can be delayed drug induced liver injury, the clinical picture suggests the liver enzyme elevations were not study treatment-related, but were manifestations of the subject's comorbidities and concomitant medications.

This placebo-controlled, double-blind study of ivosidenib in combination with azacitidine compared to matched placebo in combination with azacitidine provides a tolerable and manageable safety profile for subjects with previously untreated IDH1 mutated AML.

Conclusion

These clinically meaningful results in this extremely rare disease, supported by the established safety of ivosidenib in patients with hematologic malignancies and solid tumors, demonstrate ivosidenib in combination

with azacitidine is a safe and effective targeted therapy for patients with previously untreated IDH1 mutation-positive AML who are considered appropriate candidates for non-intensive therapy.
Date of Report: 08 December 2021