2. SYNOPSIS

Name of Sponsor/Company: Agios Pharmaceuticals, Inc.	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, Randomized, Double Blind, Placebo-Controlled Study of AG-120 in Previously Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation

Principal Investigator: [redacted]

Study center(s):

A total of 49 study sites participated in this study, with 26 sites in the United States (US), 6 sites in South Korea, 5 sites in the United Kingdom, 5 sites in Spain, 4 sites in France, and 3 sites in Italy.

Publications (reference):

Abou-Alfa GK, Macarulla Mercade T, Javle M, Kelley RK, et al. ClarIDHy: A global, phase III, randomized, double-blind study of ivosidenib (IVO) vs placebo in patients with advanced cholangiocarcinoma (CC) with an isocitrate dehydrogenase 1 (IDH1) mutation. Ann Oncol. 2019;30(suppl 5):v872.

Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): A multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(6):796-807.

Abou-Alfa GK, Valle JW, Kelley RK, Goyal L, et al. ClarIDHy: A phase 3 multicenter randomized, double-blind study of AG-120 versus placebo in patients with non-resectable or metastatic cholangiocarcinoma with an IDH1 mutation. J Clin Oncol. 2018;36(suppl 4S):TPS545.

Aguado E, Abou-Alfa GK, Zhu AX, Macarulla T, et al. IDH1 mutation detection in plasma circulating tumor DNA (ctDNA) and association with clinical response in patients with advanced intrahepatic cholangiocarcinoma (IHC) from the phase III ClarIDHy study. J Clin Oncol. 2020;38(15_suppl):Abstract 4576.

Chamberlain CX, Andrae DA, Jiang L, Gliser C, et al. Health-related quality of life in patients treated with ivosidenib for mutant-IDH1 cholangiocarcinoma: Results from ClarIDHy. Accepted for presentation at the Cholangiocarcinoma Foundation Annual Conference; 22-24 Jul 2020; Online.

Fan B, Abou-Alfa GK, Zhu AX, Pandya SS, et al. Pharmacokinetics/pharmacodynamics (PK/PD) of ivosidenib in patients with mutant IDH1 advanced cholangiocarcinoma from the phase III ClarIDHy study. J Clin Oncol. 2020;38(suppl 4):539.

Lowery MA, Abou-Alfa GK, Valle JW, Kelley RK, et al. ClarIDHy: A phase 3 multicenter randomized, double-blind study of AG-120 vs placebo in patients with an advanced cholangiocarcinoma with an IDH1 mutation. J Clin Oncol. 2017;35(15 suppl):TPS4142.

Macarulla T, Zhu AX, Javle M, Kelley RK, et al. ClarIDHy: A phase III, randomized, double-blind study of ivosidenib vs placebo in patients with advanced cholangiocarcinoma. Accepted for presentation at the Cholangiocarcinoma Foundation Annual Conference; 22-24 Jul 2020; Online.

Studied period (years):	**Phase of development:**
Date first subject enrolled: 20 February 2017 Date last subject completed: N/A, study is ongoing	3

Objectives:

Primary:

- To demonstrate the efficacy of ivosidenib based on progression-free survival (PFS) per Independent Radiology Center (IRC) assessment compared to placebo in subjects with nonresectable or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation.

Secondary:

- To evaluate the safety and tolerability of ivosidenib compared to placebo.
- To evaluate PFS per Investigator assessment.
- To compare the efficacy of ivosidenib with placebo based on overall survival (OS), objective response rate, duration of response, and time to response, with response assessed per Investigator and by the IRC.
- To evaluate health-related quality of life (HRQOL) with ivosidenib compared to placebo as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30 and EORTC QLQ-BIL21), the Patient Global Impression of Change (PGI-C), and the Patient Global Impression of Severity (PGI-S).
- To evaluate health economic outcomes as assessed by the 5-level European Quality of Life 5 Dimensions 5 Levels questionnaire (EQ-5D-5L).
- To evaluate the pharmacokinetics (PK) of ivosidenib.
- To evaluate the PK/pharmacodynamic (PD) relationship of ivosidenib and 2-hydroxyglutarate (2-HG) in blood samples.

Exploratory:

- To evaluate, for the subgroup of placebo subjects who had crossed over to the ivosidenib arm, the time from first dose of ivosidenib to second documented progression on ivosidenib or death, whichever occurred first.
- To correlate baseline molecular and/or protein characteristics in tumor tissues with clinical response.
- To correlate baseline 2-HG levels in plasma samples with clinical response.
- To evaluate levels of mutant IDH1 and other genes in circulating tumor DNA obtained from plasma at baseline and over the course of the treatment.
- To correlate any PK variations with drug-metabolizing enzyme related genes, if the data were warranted.
- To explore additional biomarkers in blood for morphologic, functional, biologic, epigenetic, and metabolic changes over the course of treatment.

Methodology:

Study AG120-C-005 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of orally administered ivosidenib in subjects with advanced cholangiocarcinoma (nonresectable or metastatic). Subjects were required to have a histologically consistent diagnosis of IDH1 gene-mutated cholangiocarcinoma (IDH1 mutation confirmed by a central laboratory) that was not eligible for curative resection, transplantation, or ablative therapies. Subjects had to have documented progression of disease and had received treatment with at least 1 but not more than 2 prior treatment regimens for advanced disease (nonresectable or metastatic). At least 1 of the prior

regimens must have included gemcitabine or 5-fluorouracil (5-FU). Systemic adjuvant chemotherapy was considered a line of treatment if there was documented disease progression during or within 6 months of completing the therapy, with Sponsor approval.

Following confirmation of eligibility in the pre-screening and pre-treatment/screening periods, a total of approximately 186 subjects were planned to be randomized in a 2:1 ratio to receive ivosidenib orally at a dose of 500 mg once daily (QD) or ivosidenib-matched oral placebo QD, respectively. Randomization was stratified by number of prior systemic therapies in advanced setting (1 versus 2). Cycles were 28 days (± 2 days) in duration, and dosing was continuous. All subjects continued to receive best supportive care according to institutional practice throughout the study, regardless of treatment arm. Study visits were conducted every other week during Cycles 1-3 (Days 1 and 15), and Day 1 of each cycle thereafter. An end of treatment (EOT) Visit was performed on the last day of study treatment (within 5 to 33 days of last dose, to accommodate for potential dosing delays of up to 28 days). A Post-Treatment Follow-Up Visit for safety occurred 28 days (no more than 33 days) after the last dose of study drug. Every effort was made to perform protocol-specified evaluations unless consent to participate in the study was withdrawn.

Radiographic assessment (computed tomography [CT] or magnetic resonance imaging [MRI]) for evaluation of disease response was conducted every 6 weeks (±5 days) for the first 8 assessments (ie, through week 48) and every 8 weeks (±5 days) thereafter from Cycle 1, Day 1 (C1D1), independent of dose delays and/or dose interruptions, and/or at any time when progression of disease was suspected. For subjects who discontinued study drug/placebo for reasons other than disease progression or start of another anticancer agent, an assessment was conducted at the EOT Visit. Target and non-target lesion selection and objective tumor response assessments per Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1) were performed by the institutional radiologist(s). An independent central review of response was conducted by an IRC per RECIST v1.1. All scans were sent to the IRC as detailed in the site-specific Imaging Core Manual.

Assessments for HRQOL (EORTC QLQ-C30, EORTC QLQ-BIL21, PGI-C, and PGI-S), health economic outcomes (EQ-5D-5L), and compliance, as well as blood sampling for PK/PD assessments and blood and plasma sampling for exploratory biomarker and correlative studies, were conducted as outlined in the Schedule of Assessments.

Adverse events (AEs) and concomitant medications were monitored throughout the study, starting from the first dose of study treatment. Toxicity severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Subjects also underwent evaluations for hematology and serum chemistry, coagulation testing, urinalysis, Eastern Cooperative Oncology Group performance status (ECOG PS), physical examinations, vital signs, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) (by echocardiography [ECHO] or other methods according to institutional practice, performed according to institutional standard of care, only if clinically indicated) as outlined in the Schedule of Assessments.

An independent data monitoring committee reviewed the safety data on a regular basis to ensure the safety of treatment and proper conduct of the study. The first interim safety review meeting was conducted when approximately 20 subjects completed 2 cycles of therapy or discontinued earlier; thereafter, meetings were conducted every 3-6 months or on an ad-hoc basis. No formal interim analysis for efficacy was conducted before the primary analysis.

Subjects continued with their assigned study treatment until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, the subject was lost to follow-up, or the Sponsor unblinded or ended the study, whichever occurred first.

Upon request by the Investigator, the subjects and site staff were unblinded to treatment assignment after the documented disease progression (as assessed by the Investigator) was reviewed and approved by the Sponsor Medical Monitor. Subjects randomized to the placebo arm who continued to meet eligibility criteria determined in the EOT visit were given the opportunity to cross over to the

active treatment arm (starting at C1D1) and receive ivosidenib. These subjects continued to be evaluated for tumor response by the Investigator, per protocol. If the treatment assignment was determined to be ivosidenib upon radiographic disease progression, the Investigator in consultation with the Sponsor, may have considered continuing treatment with ivosidenib, provided the subject was clinically benefitting and there was no contraindication to continuing treatment beyond progression.

Subjects who discontinued study treatment for reasons other than disease progression or withdrawal of consent were followed in PFS follow-up (every 6 weeks through week 48, and every 8 weeks thereafter) until documented disease progression or the initiation of new cancer therapy. If subjects began a new anticancer therapy during PFS follow-up, information on the new anticancer therapy was collected. The primary analysis of PFS occurred once 131 PFS events had been determined by Investigator assessment and is reported in the primary clinical study report (CSR).

OS follow-up assessments occurred approximately every 12 weeks after EOT unless the subject was in PFS follow-up at that time. If a subject progressed or did not come back for scans while in PFS follow-up, then the OS follow-up assessments began at the next planned OS follow-up time point, following the schedule of every 12 weeks after EOT. Overall survival follow-up was to continue until all subjects died, withdrew consent, were lost to follow-up, or until the occurrence of 150 OS events, whichever occurred first. OS was to be analyzed twice, once at the time of PFS primary analysis, as reported in the present CSR, and once at the occurrence of 150 OS events (approximately 24 months after the last subject was randomized).

Final OS Analysis

As prespecified in the protocol and statistical analysis plan (SAP), the final analysis of PFS and other tumor response endpoints occurred once 131 PFS events had been determined by Investigator assessment. The associated data cutoff date was 31 January 2019. The primary CSR presented the final analysis results for tumor response endpoints, the interim analysis results for OS, and the results for other endpoints based on the 185 subjects who had been randomized to either ivosidenib or placebo by the time of the data cutoff date. At the time of the data cutoff date for the primary CSR, 46 subjects remained on treatment and 134 subjects had discontinued study treatment.

The purpose of this CSR addendum is to summarize updated disposition, protocol deviations, demographics and baseline characteristics, OS, health-related quality of life (HRQOL), and safety results from Study AG120 C 005 based on a data cutoff date of 31 May 2020.

Sections of the primary CSR that are affected by these new data are presented below.

Number of subjects (planned and analyzed):

Planned:

A total of approximately 186 subjects (124 ivosidenib, 62 placebo) were planned for enrollment in the study.

Analyzed:

The data cutoff date for this CSR addendum is 31 May 2020. Two subjects were randomized in the study after the data cutoff date (31 January 2019) for the primary CSR (final analysis of PFS and tumor response endpoints). Both subjects were randomized to ivosidenib and dosed; a total of 187 subjects were randomized: 126 subjects to ivosidenib and 61 subjects to placebo. Enrollment was completed on 01 March 2019.

- 187 (100.0%) subjects were included in the Intent-to-Treat (ITT) set.
- 182 (97.3%) subjects were included in the Safety Analysis Set (SAS).
- 43 (23.0%) subjects were included in the Crossover Set (COS).

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria:

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

1. ≥18 years of age.
2. Had a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) consistent with nonresectable or metastatic cholangiocarcinoma and were not eligible for curative resection, transplantation, or ablative therapies.
3. Had documented IDH1 gene-mutated disease (from a fresh tumor biopsy or the most recent banked tumor tissue available) based on central laboratory testing (R132C/L/G/H/S mutation variants tested).
4. Had an ECOG PS score of 0 or 1.
5. Had an expected survival of ≥3 months.
6. Had at least one evaluable and measurable lesion as defined by RECIST v1.1. Subjects who had received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) were eligible provided measurable disease fell outside of the treatment field or within the field and had shown ≥20% growth in size since post-treatment assessment.
7. Had documented disease progression following at least 1 and no more than 2 prior systemic regimens for advanced disease (nonresectable or metastatic). Subjects had to receive at least 1 gemcitabine- or 5-FU-containing regimen for advanced cholangiocarcinoma. Systemic adjuvant chemotherapy was considered a line of treatment if there was documented disease progression during or within 6 months of completing the therapy.
8. Had recovered from toxicities associated with prior anticancer therapy to baseline unless stabilized under medical management.
9. Had adequate bone marrow function as evidenced by:
   a. Absolute neutrophil count ≥1,500/mm^3 or 1.5 ×10^9/L
   b. Hemoglobin ≥8 g/dL
   c. Platelets ≥100,000/mm^3 or 100 × 10^9/L
10. Had adequate hepatic function as evidenced by:
    a. Serum total bilirubin ≤2 × upper limit of normal (ULN), unless considered due to Gilbert's disease
    b. Aspartate aminotransferase and alanine aminotransferase ≤5 × ULN
11. Had adequate renal function as evidenced by:
    a. Serum creatinine <1.5 × ULN

       OR

    b. Creatinine clearance ≥50 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation:

       (140 − Age) × (weight in kg) × (0.85 if female)/72 × serum creatinine
12. Was able to understand and willing to sign the informed consent form and to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling and urine sampling, during the study. A legally authorized representative could have consented on behalf of a subject who was otherwise unable to provide informed consent if acceptable to and approved by the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC). (Subjects who did not speak one of the languages that the EORTC QLQ-C30, EORTC QLQ-BIL21, PGI-C, PGI-S, or EQ-5D-5L

were provided in at this time were permitted to enroll and not complete these HRQOL/health economic outcome instruments, assuming all other eligibility criteria were met.)

13. Female subjects with reproductive potential had to 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. Females of 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 (ie, who had not menstruated) for at least 24 consecutive months (ie, did not have menses at any time in the preceding 24 consecutive months). Women of reproductive potential, as well as fertile men and their partners who were female with reproductive potential, had to agree 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. 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.

Exclusion Criteria:

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

1. Received a prior isocitrate dehydrogenase (IDH) inhibitor.
2. Received systemic anticancer therapy or investigational agent <2 weeks prior to Day 1 (washout from prior immune based anticancer therapy was 4 weeks). In addition, the first dose of study treatment should not have occurred before a period ≥5 half-lives of the investigational agent has elapsed.
3. Received radiotherapy to metastatic sites of disease <2 weeks prior to Day 1.
4. Underwent hepatic radiation, chemoembolization, and radiofrequency ablation <4 weeks prior to Day 1.
5. Had known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases were eligible if they had completed their treatment and had recovered from the acute effects of radiation therapy or surgery prior to study entry, had discontinued corticosteroid treatment for these metastases for at least 4 weeks and had radiographically stable disease for at least 3 months prior to study entry. Note: up to 10 mg per day of prednisone equivalent was allowed.
6. Had a history of another primary cancer, with the exception of: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid or liquid tumor with no known active disease present that, in the opinion of the Investigator, did not affect subject outcome in the setting of current cholangiocarcinoma diagnosis.
7. Underwent major surgery within 4 weeks of Day 1 or had not recovered from post-surgery toxicities.
8. Were pregnant or breastfeeding.
9. Were taking known strong cytochrome P450 (CYP)3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they could have been transferred to other medications within ≥5 half-lives prior to dosing.
10. Exclusion criterion 10 was removed in Protocol Amendment 4, Version 5.0
11. Had an active infection requiring systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of Day 1 (at the discretion of the Investigator, subjects with tumor fever may have been enrolled).

12. Had any known hypersensitivity to any of the components of ivosidenib or the matched placebo.
13. Had significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) Class III or IV congestive heart failure; myocardial infarction; unstable angina; and/or stroke.
14. Had LVEF <40% by ECHO scan (or by other methods according to institutional practice) obtained within 28 days prior to the start of study treatment.
15. Had a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) ≥450 msec or other factors that increased the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome). Bundle branch block and prolonged QTcF interval were permitted with approval of the Medical Monitor.
16. Were taking medications that were known to prolong the QT interval, unless they could have been transferred to other medications within ≥5 half-lives prior to dosing or unless the medications could have been properly monitored during the study. (If equivalent medication was not available, QTcF was to be closely monitored.)
17. Had known active hepatitis B (HBV) or hepatitis C (HCV) infections, known positive human immunodeficiency virus (HIV) antibody results, or AIDS related illness. Subjects with a sustained viral response to HCV or immunity to prior HBV infection were permitted. Subjects with chronic HBV that was adequately suppressed per institutional practice were permitted.
18. Had any other acute or chronic medical or psychiatric condition, including recent (within 12 months of Day 1) or active suicidal ideation or behavior, or a laboratory abnormality that could increase the risk associated with study participation or investigational product administration or could interfere with the interpretation of study results and, in the judgment of the Investigator, made the subject inappropriate for entry into this study.
19. Had known active inflammatory gastrointestinal disease, chronic diarrhea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment was allowed (assuming no drug interaction potential).
20. Had been committed to an institution by virtue of an order issued either by the judicial or administrative authorities.
21. Were dependent on the Sponsor, Investigator, or study site, per local institution regulations.

Investigational product, dosage and mode of administration, batch number:

AG-120 was provided as an oral QD continuous dose of 500 mg. Placebo was supplied as matched tablets to be administered orally.

Daily treatment with ivosidenib or placebo was started on C1D1; clinical observations were conducted over 4 hours following the first dose of study treatment on C1D1. Dosing was continuous; there were no planned inter-cycle rest periods.

In addition to the lot numbers listed in the primary CSR, 5 new lots were used between the 31 January 2019 and 31 May 2020 data cutoff dates:

AG0956, AG0957, AG0958, AG0959, AG1129

Duration of treatment:

Subjects were permitted to continue with their assigned study treatment until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, until the subject withdrew consent, was lost to follow-up, or the Sponsor ended the study, whichever occurred first. For subjects who were determined to be on AG-120 upon radiographic disease progression and demonstrate clinical benefit, Principal Investigators (PIs), with consult from the Sponsor, could keep the subjects on AG-120 after the disease progression.

Reference therapy, dose and mode of administration, batch number:

Subjects randomized to placebo received AG-120-matched placebo tablets, which were administered orally on the same schedule as AG-120.

Criteria for evaluation:

The purpose of this CSR addendum is to summarize updated disposition, protocol deviations, demographics and baseline characteristics, OS, HRQOL, and safety results from Study AG120-C-005 based on a data cutoff date of 31 May 2020. Tumor response data as assessed by the investigator continued to be collected after the final PFS analysis and are listed. Tumor response analyses were not updated.

Efficacy:

Serial radiographic evaluations (CT or MRI) to determine response to treatment based on RECIST v1.1. All scans will be sent to the IRC, as detailed in the site-specific Imaging Core Manual. The EORTC QLQ-C30, EORTC QLQ-BIL21, PGI-C, and PGI-S will assess HRQOL and the EQ-5D-5L will assess health economic outcomes.

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 will be assessed by the NCI CTCAE version 4.03.

Statistical methods:

Summary statistics were presented by treatment and scheduled visit, unless stated otherwise.

Unless otherwise specified, descriptive statistics for continuous data included the number of subjects with data to be summarized (n), mean, standard deviation, median, and minimum and maximum. Descriptive statistics for categorical/qualitative data included frequency counts and percentages. The total number of subjects in the treatment arm was used as the denominator for percent calculations, unless stated otherwise.

Descriptive statistics associated with time-to-event analyses included the number of events, the number of subjects censored, 25% quartile, median, 75% quartile, and 95% CI for median. These statistics were presented for all time-to-event analyses, unless stated otherwise.

Listings were provided for selected endpoints.

Unless specified otherwise, longitudinal data were presented by 'before crossover' and 'after crossover', defined as:

- **'**After crossover' contained data collected after placebo subjects crossed over to ivosidenib. Crossover set (COS) was the analysis set.
- 'Before crossover' contained everything else. This included
    - Data from double-blinded until the radiographic progression

- Data after radiographic progression and subsequent unblinding where ivosidenib subjects were allowed to continue staying on ivosidenib if they were clinically benefiting, and placebo subjects were not crossover if they were no longer eligible or withdrew consent

The following subject populations (ie, analysis sets) were planned, as outlined in the protocol and study SAP, and were used for presentation of the data:

- ITT: All subjects who were randomized, with the treatment arm designated according to the randomization. The ITT was the primary analysis set for all analyses except for safety.
- Safety Analysis Set (SAS): All subjects who received at least one dose of study drug (ivosidenib or placebo). Subjects were analyzed according to the actual treatment received. If a subject received at least one ivosidenib dose in before crossover period, the actual treatment for this subject was considered as ivosidenib throughout. The same rule applied to after crossover period. The Safety Analysis Set was the primary analysis set for all safety analyses.
- Per-Protocol Set (PPS): All subjects in ITT who did not violate the terms of the protocol in a way that would significantly affect the study outcome, with treatment arm designated according to the randomization.

  In general, subjects who met the following criteria were excluded from this analysis set:
  - Did not have histopathologically diagnosed nonresectable or metastatic cholangiocarcinoma.
  - Did not have documented IDH1 gene-mutated disease based on central laboratory testing.
  - Did not have any measurable lesion as defined by RECIST v1.1 as determined by IRC.
  - 3 or more prior systemic therapy in an advanced setting (nonresectable or metastatic) as defined in the protocol.
  - Had received a prior IDH inhibitor.
- COS: A subset of placebo subjects who crossed over and receive ivosidenib upon the radiographic PD. The COS was the analysis set for analyzing post-crossover data.

Treatment-emergent adverse events (TEAEs) were defined as any AEs that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, unless otherwise specified. The severity was graded based on the NCI CTCAE. All AEs were listed. Only TEAEs were summarized and referred to as AEs hereafter.

Final OS Analysis

To control the overall Type 1 error rate at the 1-sided 0.025 significance level, a fixed sequence testing procedure was used. Progression-free survival based on IRC review was tested first and, if significant, OS could then be tested based on a 2-look group-sequential design with Gamma family (-8) α-spending function to determine the efficacy boundary. The final analysis result for PFS based on IRC review was statistically significant (1-sided p-value<0.0001); therefore, OS could be statistically tested. The interim analysis (IA) for OS occurred at the time of the final analysis for PFS based on IRC review and since statistical significance was not reached for OS at the IA based on the pre-specified α-spending function, the final analysis for OS occurred, as planned, after 150 deaths were observed in the study using a 1-sided $\alpha=0.025$ adjusted for the α spent at the time of the IA.

Results Summary and Conclusions

Two subjects were randomized in the study after the data cutoff date (31 January 2019) for the primary CSR (final analysis of PFS and tumor response endpoints). Both subjects were randomized to ivosidenib and dosed; a total of 187 subjects were randomized: 126 subjects to ivosidenib and 61 subjects to placebo. Enrollment was completed on 01 March 2019. A total of 13 subjects remained on ivosidenib treatment in Study AG120-C-005 (5 subjects assigned to placebo who crossed over to

ivosidenib and 8 subjects originally assigned to ivosidenib). Among subjects who were randomized to and received ivosidenib (N=123) or placebo (N=59), the most common reason for treatment discontinuation was progression of disease in 74.8% and 86.4%, respectively.

Efficacy

The data cutoff date for the final OS analysis was 31 May 2020, at which time 150 OS events had occurred. Based on these mature data, a survival benefit was observed in favor of ivosidenib, albeit not statistically significant (HR = 0.79; 95% CI: 0.56, 1.12; 1-sided p value = 0.093). These results should be taken in context of the large proportion (70.5%) of subjects in the placebo arm who crossed over to receive ivosidenib following radiographic disease progression. The rank preserving structural failure time (RPSFT) model crossover from the placebo arm to ivosidenib arm, suggesting an improvement in OS for ivosidenib compared to placebo with a HR=0.49 (95% CI: 0.34, 0.70) and a 1-sided p-value <0.0001. The median OS for placebo after adjusting for the effect of crossover was 5.1 months.

HRQOL

Mixed-effect model with repeated measures (MMRM) analyses were conducted on the change from baseline between arms for all subscales of the EORTC QLQ-C30 and EORTC QLQ-BIL21. Subscales corresponding to physical functioning (PF), pain, and appetite loss were prespecified in the SAP. Results based on data from the 31 May 2020 data cutoff are described below. The analyses focused on data from subjects randomized to the placebo arm in the period before crossover and the ivosidenib arm. The results focus on Cycle 2, Day 1 and Cycle 3, Day 1, considering the availability of the HRQOL data. P-values were not adjusted for multiplicity.

EORTC QLQ-C30 Cycle 2, Day 1 change scores were available for 67 ivosidenib subjects and 21 placebo subjects; QLQ-BIL21 Cycle 2, Day 1 change scores were available for 65 ivosidenib subjects and 20 placebo subjects. Based on data from the 31 May 2020 data cutoff, at Cycle 2, Day 1, subjects in the ivosidenib arm generally had preserved scores from baseline on these subscales compared with subjects in the placebo arm who experienced declines (indicating worsening) on the EORTC QLQ-C30 PF and Emotional Functioning subscales and increase (indicating worsening) in EORTC QLQ-BIL21 Anxiety symptoms (all 2-sided P<0.050). The decline in PF was clinically meaningful in the placebo arm at Cycle 2, Day 1, based on the threshold estimated using anchor-based methods, while meaningful change of PF was not observed in the ivosidenib arm. At Cycle 3, Day 1, the findings on EORTC QLQ-C30 PF and Emotional Functioning subscales were sustained (ivosidenib, N=50; placebo, N=9; both 2-sided P<0.050), while no difference between arms was observed for EORTC QLQ-BIL21 Anxiety symptoms.

Subjects in the placebo arm experienced more worsening of pain symptoms compared with the ivosidenib arm at Cycle 2, Day 1 based on the EORTC QLQ-C30 Pain subscale (2-sided P=0.039), although no difference between arms was observed at Cycle 3, Day 1. Changes from baseline for the EORTC QLQ-BIL21 Pain subscale and EORTC QLQ-C30 and EORTC QLQ BIL21 subscales pertaining to appetite loss were not notably different between arms.

Changes from baseline on HRQOL scores favored ivosidenib. The data suggest subjects in the ivosidenib arm experienced preservation of PF and emotional functioning through Cycle 3, Day 1 compared with subjects in the placebo arm who experienced decline.

Safety

The safety profile of ivosidenib in subjects with cholangiocarcinoma was expected and consistent with that of the known safety profile in hematologic malignancies. Electrocardiogram QT prolongation and peripheral neuropathy are shared AEs in these two populations. In subjects with cholangiocarcinoma, electrocardiogram QT prolongation (7.8%) and peripheral neuropathy (4.8%) were among the commonly reported AEs in ivosidenib-treated subjects; however, the majority of

these events were low grade and neither of these AEs led to treatment discontinuation. Furthermore, no subject experienced ventricular tachycardia or clinically meaningful arrhythmia. In ivosidenib-treated subjects, electrocardiogram QT prolongation was primarily nonserious, low grade, and manageable with dose interruptions and dose modifications; Grade 3 AEs were infrequent (1.2%) in ivosidenib-treated subjects vs. none in placebo. Grade 4 or 5 QT prolongation AEs were not reported in any subject. Three (23.1%) of the ivosidenib-treated subjects with an AE of electrocardiogram QT prolongation concomitantly received medications known to prolong QT interval (ondansetron and/or propofol) and 1 placebo-treated subject (50%) concomitantly received fluconazole. All ivosidenib-treated subjects experiencing a QT prolongation AE had relevant medical history including cardiac (hypertension), metabolism disorders (dyslipidemia), or endocrine disorders (hypothyroidism or thyroidectomy); 2 subjects had a history of hypomagnesemia, 1 of which experienced a serious Grade 2 medically significant electrocardiogram QT prolongation event that resulted in dose modification. All placebo-treated subjects also had relevant medical history (sinus bradycardia, hypercholesterolemia, or hypertension). Fourteen ivosidenib-treated subjects experienced peripheral neuropathy (N= 8), peripheral sensory neuropathy (N=5), or paresthesia (N=1). All were low grade (2 subjects had Grade 2 AEs, the other 12 had Grade 1 AEs), nonserious, and manageable. Only 1 subject (Grade 1 AE) required dose modification. Notably, 11 of the 14 subjects (78.6%) had prior exposure to a platinum-based chemotherapy and 6 (42.9%) had a medical history of neuropathy.

AEs that were not previously recognized in hematologic malignancies but were among the commonly reported in ivosidenib-treated subjects with cholangiocarcinoma included anemia, ascites, decreased appetite, hypertension, and white blood cell count decrease. A number of the AEs were confounded and considered as manifestations of underlying medical history, disease under study, and/or intercurrent illness. While anemia was among the commonly reported AEs (18.1% vs. 5.1% in ivosidenib- and placebo-treated subjects, respectively), it is notable that the patient population in this study was previously treated with myelosuppressive therapy (platinum, gemcitabine, and/or 5-FU-based chemotherapy) and was eligible to enter study with Grade 1 or 2 anemia (hemoglobin ≥8 g/dL). Baseline data showed that 76.7% of ivosidenib treated subjects who had experienced an anemia TEAE had Grade 1 or Grade 2 anemia at baseline vs. 66.7% in placebo-treated. The majority of the events were Grade 1 and Grade 2. The incidence of Grade 3 anemia in ivosidenib-treated subjects was 7.2% vs. none in placebo-treated subjects. Grade 4 or Grade 5 anemia was not reported in any subject. Seven (23.3%) of the ivosidenib-treated subjects with an AE of anemia received blood transfusions vs. none in placebo. Ivosidenib was infrequently held due to anemia (1.2% in ivosidenib-treated subjects vs. none in placebo-treated subjects); no subject required a dose modification, and no event resulted in permanent discontinuation of treatment. In ivosidenib-treated subjects with an AE of anemia, 70% of events occurred in the context of other relevant concurrent AEs such as, hemorrhage (gastrointestinal, hepatic, and rectal), renal failure, and underlying infection.

Approximately 39.4% (13 of 33 subjects) vs. 66.7% (6 of 9 subjects) in the ivosidenib-treated and placebo-treated subjects, respectively, experiencing an AE of ascites had a medical history of ascites and/or ascites at baseline. Additional confounding factors in 7 (21.2%) of the 33 ivosidenib-treated subjects and 1 (12%) of 9 placebo-treated subjects included medical history of abdominal distension, drain or port placement, portal vein thrombosis, and biliary cirrhosis. The incidence of ≥Grade 3 and serious ascites AEs was 9.0% and 2.4% vs. 6.8% and 3.4% in the ivosidenib-treated and placebo-treated arms, respectively.

Decreased appetite, hypertension, and white blood cell count decreased were also more frequently reported in ivosidenib-treated subjects. AEs of decreased appetite were nonserious and did not appear to impact weight loss in a clinically meaningful way. Decreased appetite was infrequently (1.2%) reported as ≥Grade 3 in ivosidenib-treated subjects, and no ≥Grade 3 AEs of decreased appetite were reported in placebo-treated subjects. In ivosidenib-treated subjects, concurrent gastrointestinal AEs (abdominal pain, ascites, nausea, diarrhea) were reported in the context of decreased appetite. Eleven

(73.3%) of the 15 ivosidenib-treated subjects with an AE of hypertension had a history of hypertension, including 1 subject with pre-hypertension, vs. 1 of the 2 placebo-treated subjects (50%). The incidence of Grade 3 AEs of hypertension was low (3%) in ivosidenib-treated subjects vs. 1.7% of placebo-treated subjects. All ivosidenib- and placebo-treated subjects experiencing a ≥Grade 3 AE of hypertension had received prior and/or concomitant antihypertensive medications such as betablockers, calcium channel blockers, or angiotensin II receptor blockers. No serious AEs of hypertension were reported in any subject. Other relevant history reported in ivosidenib-treated subjects included hyperlipidemia/ cholesterolemia, coronary artery disease, and stent placement. Grade 4 and Grade 5 AEs of hypertension were not reported in any subject. White blood cell count decreased was nonserious, low grade, and infrequently (1.2%) reported as Grade 3. No Grade 3 events were reported in placebo-treated subjects, and Grade 4 or Grade 5 AEs were not reported in any subject. White blood cell count decreased did not appear to be clinically associated with the incidence of sepsis and pneumonia AEs. Seven (63.6%) of the 11 ivosidenib treated subjects with an AE of white blood cell count decreased had a concurrent AE of anemia, lymphocyte count decreased, neutrophil count decreased, and/or platelet count decreased vs. 1 (100%) placebo-treated subject.

Apart from the differences noted above, the AEs in this study were consistent with those reported in the current IB and USPI. In this analysis of this placebo-controlled, double-blind study, treatment with ivosidenib provided a favorable benefit-risk profile for locally advanced or metastatic cholangiocarcinoma patients who have received at least 1 prior therapy.

Conclusions

The primary CSR (data cutoff date 31 January 2019) reported the results of the final analyses of PFS and other tumor response endpoints. There was a statistically significant improvement in PFS based on IRC assessment for subjects randomized to ivosidenib versus subjects randomized to placebo (HR = 0.37; 95% CI: 0.25, 0.54; 1-sided p-value<0.0001); the median PFS was 2.7 months (95% CI: 1.6, 4.2) among subjects randomized to ivosidenib and 1.4 months (95% CI: 1.4, 1.6) among subjects randomized to placebo.

This CSR addendum reports the results of the final OS analysis, which was planned to occur once 150 events had been observed, based on a data cutoff date of 31 May 2020. In addition, updated safety data were provided. An improvement in OS, albeit not statistically significant (1-sided p = 0.093), was observed for subjects randomized to ivosidenib compared with subjects randomized to placebo (HR = 0.79; 95% CI: 0.56, 1.12), further supporting the clinical benefit of ivosidenib compared with placebo in this population with no approved therapies. This result should be interpreted in the context of 70.5% crossover from placebo to ivosidenib upon radiographic disease progression; additional prespecified analyses performed using the RPSFT model to take crossover into account further support that ivosidenib may improve OS (1-sided p<0.0001, HR = 0.49; 95% CI: 0.34, 0.70).

The AEs reported with a higher incidence in ivosidenib-treated subjects included gastrointestinal AEs (nausea, diarrhea, vomiting, abdominal pain), hepatobiliary events (hyperbilirubinemia), fatigue, anemia, cough, peripheral neuropathy, hypertension, and laboratory abnormalities (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] increased), ascites, decreased appetite, electrocardiogram QT prolonged, blood bilirubin increased, and white blood cell count decreased. AEs reported with a higher incidence in placebo-treated subjects included constipation, asthenia, confusional state, hypercalcemia, hyponatremia, blood alkaline phosphatase increased, dyspnea, gait disturbance, dry mouth, rash maculo-papular, and arthralgia. Clinically many of these AEs could represent manifestations of advanced cholangiocarcinoma and/or intercurrent illness.

The majority (67.5%) of AEs in ivosidenib-treated subjects were non-serious vs. 76.3% in placebo-treated subjects. Of all subjects who received ivosidenib (inclusive of the crossover population), 53.0% experienced a ≥Grade 3 AE vs. 37.3% of subjects who received placebo. Among the

commonly reported ≥Grade 3 AEs in ivosidenib-treated subjects were anemia, ascites, aspartate aminotransferase increased, hyponatremia, and hypertension. In placebo-treated subjects, the commonly reported ≥Grade 3 AEs included hyponatremia, ascites, hypophosphatemia, blood alkaline phosphatase increased, asthenia, back pain, sepsis, lymphocyte count decreased, dyspnea, and hyperkalemia. These findings were consistent with the underlying disease as well as relevant medical history. Of all subjects who received ivosidenib (inclusive of the crossover population), 1.2% experienced an AE related to ivosidenib that led to treatment discontinuation vs. no subjects who received placebo.

The incidence of on-treatment deaths, defined as deaths occurring within 28 days of the last dose of study drug, was higher in ivosidenib-treated compared to the placebo-treated subjects (8 subjects [4.8%] vs. none, respectively). Detailed narratives are provided describing these fatal events, all of which were assessed as not related to study treatment and were confounded as a result of disease, comorbidities, and/or prior therapies. Importantly, there was no concerning pattern or trend (aside from disease burden) linking these fatalities.

Overall, ivosidenib use in this heavily pre-treated cholangiocarcinoma population was tolerated and manageable with standard of care and dose modifications. The tolerability is also reflected in the relatively infrequent safety-related dose modifications, discontinuations, and examples of ongoing long-term dosing in subjects with prolonged disease control. This favorable safety profile is a notable distinction from the typical severe toxicities (eg, hair loss, myelosuppression, hand-foot rash) observed with the available chemotherapy options for patients with cholangiocarcinoma. The safety findings are consistent with those outcomes that frequently occur in advanced cancer patients and are outcomes that oncologists are trained to manage in their daily practice.

These clinically meaningful results in this rare disease, supported by the established safety of ivosidenib in patients with hematologic malignancies and solid tumors, demonstrate ivosidenib is a safe and effective targeted therapy for patients with IDH1 mutation-positive locally advanced or metastatic cholangiocarcinoma who have been previously treated with gemcitabine or 5-FU-based regimens.

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