SYNOPSIS

Name of Sponsor/Company: Agios Pharmaceuticals, Inc. **Name of Finished Product:** Ivosidenib **Name of Active Ingredient:** AG-120	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

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 Centers:

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): None

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 PFS per Independent Radiology Center (IRC) assessment compared to placebo in subjects with nonresectable or metastatic cholangiocarcinoma with an 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 (ORR), duration of response (DOR), and time to response (TTR), 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 EuroQol 5-dimensions questionnaire (EQ-5D-5L).
- To evaluate the PK of ivosidenib.
- To evaluate the PK/PD relationship of ivosidenib and 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 (PFS2).
- 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 deoxyribonucleic acid (DNA) obtained from plasma at baseline and over the course of the treatment.
- To correlate any PK variations with drug-metabolizing enzyme (DME) 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 was 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 (as 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-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 QD or ivosidenib-matched oral placebo QD, respectively. Randomization was stratified by number of prior therapies (1 vs. 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 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 (CT or 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 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 RECIST v1.1 were performed by the institutional radiologist(s). An independent central review of response was conducted by an Independent Radiology Center (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 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 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 (IDMC) 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 Cycle 1, Day 1) 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 present clinical study report.

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 clinical study report, and once at the occurrence of 150 OS events (approximately 24 months after the last subject was randomized), which will be reported in a separate clinical study report.

Number of Subjects (Planned and Analyzed):

Planned:

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

Assuming a HR of 0.5 for PFS (equivalent to a median PFS of 3 months in the placebo arm versus 6 months in the ivosidenib arm, assuming an exponential distribution), a total of 131 PFS events were required to provide 96% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis using a stratified log-rank test. Based on this, a total of approximately 186 subjects were required to be randomized in a 2:1 ratio to the ivosidenib and placebo arms, respectively, assuming approximately a 22% dropout rate, an approximate 26-month randomization period, and an additional 6-month follow-up for PFS after the last subject was randomized. Therefore, the primary analysis of PFS was to occur at approximately 6 months after the last subject was randomized.

Analyzed:

As of 31 January 2019, 185 subjects have been randomized. The study is ongoing and not closed to enrollment. The following data sets were analyzed:

- 185 (100%) subjects were included in the ITT population
- 184 (99.5%) subjects were included in the PPS
- 180 (97.3%) subjects were included in the SAS
- 35 (18.9%) subjects were included in the COS

Diagnosis and Main Criteria for Inclusion:

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 (AST) and alanine aminotransferase (ALT) ≤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 QLQ-C30, 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 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 CYP3A4 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 acquired immunodeficiency syndrome (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 once daily 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.

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, 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:

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% confidence interval 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 statistical analysis plan, and were used for presentation of the data:

- Intent-to-Treat (ITT): All subjects who were randomized, with the treatment group 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 SAS 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 group 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
- Crossover Set (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.

Summary – Conclusions

As of the data cutoff date for this CSR (31 January 2019), enrollment in Study AG120-C-005 has not been completed and the study remains ongoing.

As of 31 January 2019, 185 subjects have been randomized: 124 subjects to ivosidenib and 61 subjects to placebo. In total, 180 subjects received at least 1 dose of study treatment (121 [97.6%] subjects treated with ivosidenib and 59 [96.7%] subjects with placebo); 134 (74.4%) subjects have discontinued treatment, with 46 (25.6%) remaining on treatment.

Five subjects who were randomized did not receive treatment due to deterioration of their health status according to the investigator (2 subjects) and failure to continue to meet eligibility criteria (3 subjects).

Among the subjects who received ivosidenib (N=121), the most common (≥5%) reasons for treatment discontinuation were progression of disease in 65 (53.7%) subjects, AE in 6 (5.0%) subjects, and withdrawal by subject in 6 (5.0%) subjects.

Among the subjects who received placebo (N=59), the most common (≥5%) reasons for treatment discontinuation were progression of disease in 44 (74.6%) subjects and AE in 4 (6.8%) subjects.

A greater proportion of subjects in the placebo arm (74.6%) than in the ivosidenib arm (53.7%) discontinued treatment due to progressive disease. There were no other clinically meaningful differences between the ivosidenib and placebo arms in terms of reasons for discontinuation.

Of the 61 subjects randomized to placebo, 35 (57.4%) subjects experienced progressive disease based on investigator assessment and crossed over to receive open-label ivosidenib per the protocol. At the time of the data cutoff date, 30 (85.7%) subjects had discontinued treatment, with 5 (14.3%) remaining on treatment. The most common (≥5%) reasons for treatment discontinuation among subjects who crossed over were progression of disease in 25 (71.4%) subjects, AE in 2 (5.7%) subjects, and physician decision in 2 (5.7%) subjects.

Efficacy Results:

Ivosidenib demonstrated a robust improvement in PFS compared with placebo (HR = 0.37; 95% CI: 0.25-0.54; 1-sided P <0.001). The durability of treatment effect of ivosidenib is represented by the PFS rates at 6 and 12 months of 32.0% and 21.9%, respectively, versus "not estimable" in the placebo arm (ie, no subjects in the placebo arm had PFS of ≥6 months by the data cutoff date, with the longest PFS being censored); the median PFS was 2.7 months (95% CI: 1.6-4.2) among subjects randomized to ivosidenib versus 1.4 months (95% CI: 1.4-1.6) among subjects randomized to placebo.

The PFS as assessed by the investigator was similar to that observed with IRC assessment and was also statistically significant for subjects randomized to ivosidenib versus subjects randomized to placebo (HR: 0.47; 95% CI: 0.33-0.68; P<0.001), with a median PFS of 2.7 months (95% CI: 1.6-3.6) among subjects randomized to ivosidenib and 1.4 months (95% CI: 1.4-2.5) among subjects randomized to placebo.

Partial responses were observed in 3 (2.4%) subjects randomized to the ivosidenib arm by IRC assessment, with a duration of response of ranging from 2.73 to 11.07 months. Approximately half (50.8%) of subjects randomized to ivosidenib had a BOR of SD, while 17 (27.9%) subjects randomized to placebo had a BOR of SD before crossover. The maximum treatment duration was approximately 22.5 months in the ivosidenib arm and 6.9 months in the placebo arm at the time of the primary analysis.

The median OS was 10.8 months (95% CI: 7.7-17.6) for subjects randomized to ivosidenib versus 9.7 months (95% CI: 4.8-12.1) for subjects randomized to placebo based on the ITT analysis. Although there was no statistical difference between the ivosidenib and placebo arms (HR=0.69; 95% CI: 0.44-1.10; 1-sided P=0.06) partially due to the allowance of crossover from placebo to ivosidenib upon radiographic progression, there is a trend that ivosidenib is associated with an improved OS compared with placebo. In addition, the Rank Preserving Structural Failure Time (RPSFT) model demonstrated a clear separation of the KM curves between ivosidenib and placebo arms can be seen once adjusted for the effect of crossover on the placebo arm using the RPSFT adjustment (median OS 10.8 months for ivosidenib versus 6.0 months for adjusted placebo; HR=0.46; 95% CI: 0.28-0.75; 1-sided p<0.001).

These data are further supported by the PRO data, which suggest that from baseline to Cycle 2 Day 1 ivosidenib was associated with preservation of physical function and emotional functioning compared with placebo subjects who on average had a more significant decline in these parameters. There are limited data to draw conclusions beyond the Cycle 2, Day 1 time point.

Taken together, the results demonstrate the clinical benefit of ivosidenib in patients with previously treated advanced IDH1m cholangiocarcinoma.

Pharmacokinetics/Pharmacodynamics Results:

Ivosidenib was rapidly absorbed following single and multiple QD 500 mg ivosidenib doses. Ivosidenib exposure on Cycle 2, Day 1 were higher than those on Cycle 1, Day 1, with low to moderate accumulation. Plasma ivosidenib appeared to reach steady state within the first cycle of continuous dosing.

Plasma 2-HG concentrations for subjects with cholangiocarcinoma were elevated at baseline and decreased from baseline to plasma 2-HG levels observed in healthy subjects after ivosidenib treatment for 1 cycle. Plasma 2-HG inhibition was generally maintained through the treatment period (up to 19 cycles of dosing).

Plasma ivosidenib exposure was similar following single and multiple dose administration of ivosidenib 500 mg QD to subjects with cholangiocarcinoma in this study compared with the Phase 1 Study AG120-C-002.

Safety Results:

The AG120-C-005 study demonstrated that as a single agent in patients with advanced cholangiocarcinoma, ivosidenib was generally well tolerated with a manageable safety profile.

The AEs noted more frequently in the ivosidenib regimen were generally expected, were consistent with the ivosidenib side effect profile, and were easily manageable. Of note, ivosidenib subjects in the AG120-C-005 study reported a higher frequency of hematologic AEs (ie, Anemia) and a higher frequency of GI events (ie, Diarrhea, Nausea, Ascites), Rash, and Peripheral Neuropathy in comparison with the placebo population. Of note, subjects in this study had received previous myelosuppressive therapies, and inclusion criteria permitted Grade 1-2 anemia at baseline (hemoglobin ≥8 g/dL). These safety observations did not alter the favorable benefit-risk profile of ivosidenib in the studied population.

Hepatobiliary events were reported at a higher frequency in the ivosidenib arm (N=121) than in the placebo arm (N=59)(15 [12.4%] and 2 [3.4%], respectively); Hyperbilirubinemia occurred in 6 (5.0%) ivosidenib subjects and in no placebo subjects. A significant safety concern was not identified.

Peripheral neuropathy is a known AE associated with ivosidenib. In this analysis, 9.9% (n=12) of subjects in the ivosidenib arm and no subjects in the placebo arm reported peripheral neuropathy. Ten out of 12 subjects had prior exposure to a platinum-based chemotherapy and 5 had a medical history of neuropathy. One subject with prior exposures to oxaliplatin and cisplatin chemotherapies experienced a Grade 2 neuropathy event deemed unrelated to ivosidenib that resolved to Grade 1. Three (2.5%) subjects in the ivosidenib arm had Grade 1 peripheral sensory neuropathy; 2 of these subjects had prior exposure to a platinum-based chemotherapy. No subjects reported severe (Grade 3) neuropathy, and no subjects discontinued study treatment because of peripheral neuropathy.

There were no clinically significant safety concerns with respect to the occurrence of QT prolongation, arrythmias, rash, or GI events. In addition, no safety concerns were identified across age or gender subgroups.

In this analysis of this placebo-controlled, double-blind study, treatment with ivosidenib provided a positive benefit-to-risk profile for locally advanced or metastatic cholangiocarcinoma patients who have received at least 1 prior therapy. Ivosidenib was generally well tolerated by this heavily pretreated patient population. The TEAEs in this study were consistent with the current IB and USPI and were generally expected based on clinical experience.

Conclusion:

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.

Date of Report: 20 February 2020