2. SYNOPSIS

Name of Sponsor/Company: Institut de Rechereches Internationales Servier (I.R.I.S.)	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-Fraile E, Tassinari A, Ishii Y, et al. Molecular and morphological changes induced by ivosidenib correlate with efficacy in mutant-IDH1 cholangiocarcinoma. Future Oncol. 2021;17(16):2057-2074.

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. Zhu AX, Macarulla T, Javle MM, et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. JAMA Oncol. 2021;7(11):1669–1677.	
Studied period (years): Date first subject enrolled: 20 February 2017 Date last subject completed: 17 May 2021	**Phase of development:** 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 the first CSR addendum, based on a data cutoff date of 31 May 2020, was to summarize updated disposition, protocol deviations, demographics and baseline characteristics, OS, HRQOL, and safety results from Study AG120 C 005. The purpose of this (second) CSR addendum, based on a final database lock date of 21 June 2021, was to summarize further updated disposition, protocol deviations, HRQOL, and safety results.

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:

There were 185 subjects randomized for the primary CSR (data cutoff date 31 January 2019). Two subjects were randomized in the study after that date (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. The data cutoff date for the first CSR addendum was 31 May 2020. The database lock date for this (second) CSR addendum was 21 June 2021.

- 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 (70.5%) placebo 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

No new lots were added between the 31 May 2020 data cutoff date and the 21 June 2021 database lock date.

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 the first CSR addendum, based on a data cutoff date of 31 May 2020, was to summarize updated disposition, protocol deviations, demographics and baseline characteristics, OS, HRQOL, and safety results from Study AG120-C-005. 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. The purpose of this (second) CSR addendum, based on a database lock date of 21 June 2021, was to update disposition, protocol deviations, HRQOL, and safety results.

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.

Results Summary and Conclusions

There were 185 subjects randomized for the primary CSR (data cutoff date 31 January 2019). Two subjects were randomized in the study after that date (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. As of the database lock date of 21 June 2021, all 13 subjects who had previously remained on ivosidenib treatment (from the 31 May 2020 datacut) discontinued treatment. 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 79.7% and 86.4%, respectively.

HRQOL

Due to minimal changes in data between the 31 May 2020 datacut and the 21 June 2021 database lock, there was no impact of additional HRQOL data on study results. There was also no impact of additional missing data on HRQOL data interpretation.

Safety

Since there were only minor changes to safety data for the 21 June 2021 database lock, safety conclusions remain the same as those from the first CSR addendum (11 February 2021). Subsequent analyses on the updated safety data are consistent with those reported previously and continue to support the previous safety conclusions.

Due to MedDRA versioning changes from version 23.0 used at the time of the 31 May 2020 datacut and version 23.1 used at the time of the 21 June 2021 database lock, Arthralgia is the only Preferred Term (PT) that did not previously meet the threshold to be among the most common TEAEs. Also due to coding changes, Biliary obstruction was the only PT that did not previously meet the threshold to be among the most common SAEs or leading to study drug being held; it was previously recorded as Bile duct obstruction. Overall, there were minimal changes in the incidence of TEAEs, Grade ≥3 TEAEs, and SAEs between the 31 May 2020 datacut and the 21 June 2021 database lock.

Hyperglyceamia was the only newly-occurring AE between the 31 May 2020 datacut and the 21 June 2021 database lock that had a clinically meaningful difference, showing a ≥5% difference between the ivosidenib arm (N=123) versus the placebo arm (N=59), occurring in 9 (7.3%) subjects versus 1 (1.7%) subject, respectively. Each was nonserious and low grade (Grade 1 or Grade 2). TEAEs of Hyperglyceamia were confounded on account of baseline laboratory data, medical history, and intercurrent illness. Five of the 9 subjects in the ivosidenib arm had elevated serum glucose at baseline, 2 subjects had an ongoing infection at the time of the Hyperglycaemic event (Escherichia bacteremia and influenza), 3 of the 9 subjects had a history of diabetes or hyperglycemia, and all subjects had underlying disease as a contributing factor. In addition, only 1 subject in the ivosidenib arm that had a treatment-related event, Hyperglycaemia, which was reported in a subject with multiple liver metastases and is consistent with the current patient population and previous safety conclusions.

Between the 31 May 2020 datacut through the 21 June 2021 database lock, there were no new TEAEs leading to death and no deaths assessed by the Investigator as drug-related. The overall risks of ivosidenib remained consistent with those reported in previously.

Conclusions

IDH1 mutation-positive cholangiocarcinoma is a serious and rare disease with limited effective and no approved targeted treatment options. In the absence of any approved targeted treatments, patients

with IDH1 mutation-positive locally advanced or metastatic cholangiocarcinoma who have been previously treated with gemcitabine or 5-FU-based regimens represent a population with a high unmet medical need for a safe and effective treatment option.

The primary CSR (data cutoff date 31 January 2019) reported the results of the final analyses of PFS and other tumor response endpoints. The first CSR addendum, based on a data cutoff date of 31 May 2020, reported the results of the final OS analysis, which was planned to occur once 150 events had been observed. In addition, updated safety data were provided. The current report, which is the second CSR addendum, is based on the final database lock date of 21 June 2021. Updated HRQOL as well as safety data were provided. Since changes to HRQOL data were minimal from the 31 May 2020 data cutoff and the 21 June 2021 database lock, efficacy conclusions concerning HRQOL data remained the same as for the previous CSR addendum (11 February 2021).

Overall, ivosidenib use in this heavily pre-treated cholangiocarcinoma population was tolerated and manageable with standard of care and dose modifications. 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 minimal to no changes in the incidence of TEAEs, Grade ≥3 AEs, and SAEs between the 31 May 2020 datacut and the 21 June 2021 database lock.

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. The benefit-risk profile remains positive.

Date of the report:

16 February 2022