2 SYNOPSIS

Name of Sponsor: I.R.I.S., 22 route 128 91190 GIF-SUR-YVETTE, France	*(For National Authority Use only)*
Test drug S95031 **Name of Finished Product:** TIBSOVO **Name of Active Ingredient:** Ivosidenib (formerly AG-120)	
Title of study: A Phase 2, Open-label, Multicenter Study of Orally Administered Ivosidenib in Previously Treated Japanese Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation Protocol No.: CL2-95031-008 EudraCT No.: Not applicable	
Main Investigator: Not applicable	
Study country: Japan	
Publication (reference): Not applicable	
Studied period: Initiation date: 10 October 2023 Data cutoff date: 01 October 2024 Completion date: Ongoing	**Phase of development of the study:** PHASE II

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of ivosidenib based on PFS status at 6 months per Independent Radiology Center (IRC) assessment	• Progression-free survival (PFS) status (as assessed by the IRC per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) at 6 months after Day 1 (C1D1).
Secondary	
• To evaluate the safety and tolerability of ivosidenib	• AEs, SAEs, and AEs leading to discontinuation or death. The severity of AEs was assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v5.0. • Safety laboratory parameters, vital signs, 12-lead electrocardiogram (ECGs), evaluation of left ventricular ejection fraction (LVEF), Eastern Cooperative Oncology Group (ECOG) performance status (PS), and concomitant medications.
• To evaluate the efficacy of ivosidenib on overall survival (OS), progression-free survival (PFS), objective response (OR),	• OS, defined as the time from Day 1 (C1D1) to date of death due to any cause.

duration of response (DOR), and time to response (TTR), with response assessed per Investigator and by the IRC.	• PFS, defined as the time from C1D1 to the date of first documentation of disease progression as assessed by the Investigator and by the IRC per RECIST v1.1. or death due to any cause, whichever occurred first. • OR, defined as objective response rate (confirmed complete response [CR] or confirmed partial response [PR]), as assessed by the Investigator and by the IRC per RECIST v1.1. • DOR, defined as the time from date of first documented confirmed CR or confirmed PR to date of first documented disease progression or death due to any cause, as assessed by the Investigator and by the IRC per RECIST v1.1. • TTR, defined as the time from Day 1 (C1D1) to date of first documented confirmed CR or confirmed PR for responders, as assessed by the Investigator and by the IRC per RECIST v1.1.
• To evaluate health-related quality of life (HRQOL) with ivosidenib	• HRQOL as assessed by validated instruments (EORTC-QLQ-C30, EORTC-QLQ-BIL21). • Health economic outcomes as assessed by the EQ-5D-5L instrument.
• To evaluate the PK of ivosidenib	• Serial or sparse blood sampling at specified time points for determination of plasma concentration-time profiles and PK parameters of ivosidenib.
• To evaluate the PK/PD relationship of ivosidenib and 2-hydroxyglutarate (2-HG) in blood samples	• Blood sampling at specified time points for determination of 2-HG levels to characterize the PD effects of ivosidenib.

Methodology:

This was an open-label, Phase 2, single-arm, multicenter study of orally administered ivosidenib in previously treated Japanese participants with nonresectable or metastatic IDH1 gene-mutated cholangiocarcinoma (CCA). Approximately 10 Japanese participants were planned to be enrolled in the study.

The study comprised a pre-screening period, a pre-treatment/screening period, a treatment period, a post-treatment follow-up, and a PFS and survival follow-up.

Each participant's course of treatment comprised the following periods:

Pre-Screening Period: During pre-screening, IDH1 gene mutation was to be confirmed by the central laboratory using the participant's most recent banked tumor sample (preferably from within the last 3 years) or a fresh biopsy.

Pre-Treatment/Screening Period: Participants underwent screening procedures to determine eligibility within 28 days prior to the start of study treatment on C1D1. Baseline radiographic scans were performed within 21 days prior to C1D1.

Treatment Period and End of Treatment Visit:

During the treatment period, participants who met all eligibility criteria received ivosidenib orally at a dose of 500 mg once daily (QD). Cycles were 28 days (± 2 days) in duration, and dosing was continuous. All participants received best supportive care according to institutional practice throughout the study. Study visits were conducted every week during Cycle 1 (Days 1, 8, 15, and 22), every other week during Cycles 2 and 3, and on Day 1 of each cycle thereafter.

An end of treatment (EOT) visit was conducted on the last day of the study treatment (within 5 to 33 days of the last dose, to accommodate potential dosing delays of up to 28 days).

Post-Treatment Follow-up Visit: 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. If the dose was interrupted for 28 days and the participant discontinued study participation, the EOT visit served as the post-treatment follow-up visit.

PFS and Survival Follow-up: Participants who discontinued the study treatment for reasons other than disease progression or withdrawal of consent and were alive at the EOT visit entered the PFS follow-up with the same schedule of assessments as before study treatment discontinuation until documented disease progression, initiation of new anticancer therapy, death, withdrawal of consent, lost to follow-up, or the end of study/study termination, whichever occurred first. If a participant began a new anticancer therapy during the PFS follow-up, the information on the new therapy was collected.

Overall survival follow-up assessments occurred approximately every 12 weeks after EOT unless the participant was in the PFS follow-up at that time. If a participant progressed or did not return for scans while in the 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. Overall survival follow-up was continued until all participants died, withdrew consent, were lost to follow-up, or for up to 24 months after the last participant enrolled, whichever occurred first.

The end of study (EOS) was defined as the time until all participants died, withdrew consent, were lost to follow-up, reached approximately 24 months after the last participant enrolled, or the Sponsor terminated the study, whichever occurred first.

Radiographic assessment (CT or MRI) for evaluation of disease response was conducted every 6 weeks (± 5 days) for the first 8 assessments (i.e., 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 participants who discontinued the study drug for reasons other than disease progression, withdrawal of consent, or start of another anticancer agent, an assessment was conducted at the EOT visit.

Assessments for HRQOL were conducted at pre-dose on C1D1 and on Day 1 of every cycle thereafter until EOT. After the EOT visit, the HRQOL assessments were conducted every 12 weeks until the start of new anticancer therapy. One additional HRQOL assessment was conducted at the safety follow-up visit. Health

economic outcome assessments were conducted pre-dose on C1D1, at Cycle 3 on Day 1 (C3D1), and at the EOT visit.

Participants were assessed for adverse events (AEs) and concomitant medications at every visit, starting from the first dose of study treatment. Toxicity severity was graded according to the NCI CTCAE v5.0. Additional safety assessments conducted periodically throughout the study included vital signs, physical examinations, ECOG PS, echocardiography (ECHO) (or other methods according to institutional practice) for determination of LVEF (only if clinically indicated), ECG, and clinical laboratory assessments (hematology, serum chemistry, urinalysis, coagulation, and urine pregnancy test).

Blood samples for assessment of plasma concentration of ivosidenib and 2-HG were also collected during the study.

The investigational medicinal product (IMP) of this study was ivosidenib. The IMP was supplied as 250 mg strength film-coated (blue) tablets for oral administration. The tablets contained the inactive ingredients hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, and Opadry®II Blue.

Number of participants:
Planned: 10
Included: 12

Diagnosis and main criteria for inclusion:

Inclusion criteria:

Participants were eligible to enter the study if they met all the following criteria:

1. Male or female participant aged ≥ 18 years old.
2. Had a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) consistent with nonresectable or metastatic CCA 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. Participants 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 in the 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) with progression on the treatment that was most recently given at a minimum. Participants had to receive at least 1 gemcitabine- or 5-fluorouracil (5-FU)-containing regimen for advanced CCA. 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 (GFR) estimation: (140 − Age) × (weight in kg) × (0.85 if female)/72 × serum creatinine
12. Be able to understand and willing to sign the informed consent form (ICF) 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 consent on behalf of a participant who was otherwise unable to provide informed consent if acceptable to and approved by the site's Institutional Review Board (IRB). (Participants who could not respond to the EORTC-QLQ-C30, EORTC-QLQ-BIL21, or EQ-5D-5L, are provided at that time were permitted to enroll and not complete the HRQOL/health economic outcome instruments, assuming all other eligibility criteria were met).
13. Women of childbearing potential (WOCBP) had to have a negative serum pregnancy test before the start of therapy. WOCBP were defined as having had onset of their first menstrual period and had not undergone a hysterectomy or bilateral oophorectomy or were not naturally postmenopausal (i.e., had not menstruated at all in the preceding 24 consecutive months without any other medical reasons).
    a. In case a participant was a WOCBP: the woman had to test negative in a serum pregnancy test before the start of therapy and had to use highly effective methods of birth control defined as those alone or in combination that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, combined oral contraceptives, some intra-uterine devices (IUDs), or vasectomized partner from the time of giving informed

consent throughout the study, and for 90 days after the last dose of ivosidenib. Women using hormonal contraceptive had to also use a barrier method.

b. In case participant was a man: the man had to be either vasectomized or use effective contraception. In this last case, the partner of childbearing potential had to use highly effective methods of birth control defined as those alone or in combination that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly from the time of giving informed consent throughout the study and for 90 days after the last dose of ivosidenib.

Non-inclusion criteria:

14. Received a prior IDH inhibitor.
15. Received systemic anticancer therapy or an investigational agent < 2 weeks prior to C1D1 (washout from prior immune-based anticancer therapy is 4 weeks). In addition, the first dose of study treatment should not have occurred before a period ≥ 5 half-lives of the investigational agent had elapsed.
16. Received radiotherapy to metastatic sites of disease < 2 weeks prior to Day 1.
17. Underwent hepatic radiation, chemoembolization, and radiofrequency ablation < 4 weeks prior to C1D1.
18. Had known symptomatic brain metastases requiring steroids. Participants 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.
19. Had a history of another primary cancer, with the exception of: a) curatively resected nonmelanoma 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 participant outcome in the setting of current CCA diagnosis.
20. Underwent major surgery within 4 weeks of C1D1 or had not recovered from post-surgery toxicities.
21. Pregnancy, possibility of becoming pregnant during the study and breast-feeding women, or woman who planned to restart breast-feeding after the IMP administration/intake. Note: In the case where the Investigator had assessed that the participant may have been pregnant because of medical interview, etc, the participant was excluded.
22. Were taking known strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window (refer to Appendix 6 of the study protocol [Appendix 16.1.1]) unless they could be transferred to other medications within ≥ 5 half-lives prior to dosing.
23. 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, participants with tumor fever may have been enrolled).
24. Had any known hypersensitivity to any of the components of ivosidenib.
25. 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 (refer to Appendix 7 of the study protocol [Appendix 16.1.1]); myocardial infarction; unstable angina; and/or stroke.
26. 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.

27. Had a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) (refer to Appendix 8 of the study protocol [Appendix 16.1.1]) ≥ 450 msec or other factors that increased the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome). Bundle branch block and prolonged QTcF interval were permitted with approval of the Sponsor.

28. Were taking medications that were known to prolong the QT interval (refer to Appendix 9 of the study protocol [Appendix 16.1.1]) 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 should have been closely monitored.)

29. 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. Participants with a sustained viral response to HCV treatment or immunity to prior HBV infection were permitted. Participants with chronic HBV that was adequately suppressed per institutional practice were permitted.

30. 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 have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the Investigator, would have made the participant inappropriate for entry into this study.

31. 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).

32. Had known medical history of progressive multifocal leukoencephalopathy (PML).

Test drug: Ivosidenib was provided as 250 mg strength tablets to be administered orally. Participants received 500 mg QD on Days 1 to 28 in 28-day cycles. Starting with C1D1, dosing was continuous; there were no planned inter-cycle rest periods.

Comparator (Reference product and/or placebo):
Not applicable

Duration of treatment:

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

Upon radiographic disease progression, PIs, in consultation with the Sponsor, may have kept the participants on ivosidenib after disease progression, provided the participants were clinically benefitting and there was no contraindication to continuing treatment beyond progression.

End of study was defined as the time until all participants died, withdrew consent, were lost to follow-up, approximately 24 months after the last participant enrolled, or the Sponsor had terminated the study, whichever occurred first.

Criteria for evaluation:

Efficacy measurements:

Primary efficacy endpoint:

Progression-free survival status as assessed by the IRC (RECIST v1.1) at 6 months after Day 1 (C1D1). Kaplan-Meier method was used to estimate the 6-month PFS rate.

Secondary efficacy endpoints:

Overall survival, PFS per Investigator and IRC, OR, DOR per IRC (RECIST v1.1) and per investigator, TTR per IRC (RECIST v1.1) and per investigator.

HRQOL (EORTC-QLQ-C30, EORTC-QLQ-BIL21).

Health economic outcomes as assessed by the EQ-5D-5L instrument.

Safety measurements:

Analysis of AEs, SAEs, and AEs leading to discontinuation or death.

Analysis of laboratory parameters, vital signs, 12-lead ECG, LVEF, ECOG PS, and concomitant medications.

Pharmacokinetic measurements:

Analysis of ivosidenib PK in plasma and PK/PD analyses of ivosidenib and 2-HG.

Other measurements:

Gene mutation analysis and molecular characterization.

Statistical methods:

Analysis Set:

Intent-To-Treat Set (ITT): All enrolled and treated participants, used for primary efficacy analyses. This was the default analysis set unless otherwise specified.

Safety Analysis Set (SAS): All participants who received at least one study treatment dose, used for primary safety data analysis, unless otherwise specified.

Per-Protocol Set (PPS): ITT participants without significant protocol violations (as per criteria defined in the SAP), used for sensitivity analyses of the primary endpoint.

Pharmacokinetic Analysis Set (PAS): All participants with at least one evaluable post-dose PK blood sample for ivosidenib.

Pharmacodynamic Analysis Set: All participants with at least one evaluable plasma 2-HG blood sample for ivosidenib.

Efficacy analysis:

Primary endpoint:

The primary analysis was performed on the ITT Set.

The primary endpoint was PFS status at 6 months after Day 1 (C1D1). The 6-month PFS rate was defined as the probability of participants who were alive and progression-free at 6 months after C1D1. The Kaplan-Meier method was used to estimate the 6-month PFS rate. An exact binomial test with a 1-sided significance level of 0.05 was used to compare the 6-month PFS rate against 2.6%.

Participants without documentation of disease progression or death at the time of the analysis of PFS were censored at the date of the last response assessment prior to the start of alternate therapy. Details on the handling of missing response assessments and censoring were described in the Statistical Analysis Plan (SAP).

Kaplan-Meier estimates, 95% CIs according to the Brookmeyer and Crowley method for the median, Q1 and Q3 for PFS, and probabilities of event free at selected time points (such as 3-month, 6 month, 9-month, and 12-month) were presented. Kaplan-Meier curves of PFS were provided with the number of participants at risk over time included.

Concordance of PFS between the Investigator and IRC assessment was also summarized.

Secondary endpoint:

The safety and tolerability of ivosidenib were evaluated using the SAS set.

- AEs, SAEs, AESIs, and AEs leading to discontinuation or death were collected as endpoints and assessed for their severity as per the NCI CTCAE v5.0. All TEAEs were summarized by seriousness, relationship to the study drug, reasons for dose modification, withdrawal, and categorization by frequency and MedDRA coding.
- Safety laboratory parameters, vital signs, 12-lead ECGs, LVEF, ECOG PS, and concomitant medications were also collected as safety data.

The secondary efficacy endpoints were evaluated on OS, PFS, OR, DOR, TTR assessed per Investigator and by the IRC.

- OS was analyzed from Day 1 to death from any cause. Kaplan-Meier analysis and survival rate estimation were performed, including estimates of the median and other quantiles, as well as individual time points (e.g., 3-month, 6-month, and 12-month rates).
- PFS by Investigator and by IRC was assessed per RECIST v1.1 using the same censoring rules and analysis as for the primary endpoint.
- OR was analyzed for the CR or PR by the IRC, and sensitivity analysis was performed by the investigator. ORR was derived from the best overall response (BOR).
- DOR was analyzed by the IRC, and sensitivity analysis was performed by the Investigator. If there were at least 5 responders, a Kaplan-Meier plot of DOR was to be generated.
- TTR was calculated on CR or PR. The primary analysis was done by IRC and the sensitivity analysis by the Investigator.
- HRQOL was assessed with validated instruments (EORTC-QLQ-C30, EORTC-QLQ-BIL21).
- Health economic outcomes were assessed by the EQ-5D-5L instrument.

Study participants: disposition baseline characteristics and treatments analysis and Safety analysis:
Descriptive statistics were provided.

Pharmacokinetic analysis:

Ivosidenib and 2-HG concentrations were reported with precise descriptive statistics and plotted against sampling times on linear and logarithmic scales to analyze PK and PD parameters.

SUMMARY – RESULTS-CONCLUSIONS

DISPOSITION OF PARTICIPANTS AND ANALYSIS SETS

A total of 21 participants were screened for the study; 9 of the 21 participants were screening failures due to various inclusion/exclusion criteria.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Out of the 12 enrolled participants 7 (58.3%) were males and 5 (41.7%) were females. All participants were of Asian descent and identified as non-Hispanic or Latino ethnicity. Seven (58.3%) participants were aged between 45 and 65 years, while the remaining 5 (41.7%) participants were aged 65 years and older, with a median age of 56.5 years (range: 45-80 years). The median BMI was 22.5 kg/m² (range: 17-31 kg/m²). Participants had a median weight of 58.9 kg (range: 36-88 kg)) and a median height of 159.5 cm (146-183 cm).

All 12 participants had metastatic CCA at screening, with 11 (91.7%) participants diagnosed with intrahepatic CCA and 1 (8.3%) participant with perihilar CCA at initial diagnosis. At the initial diagnosis, staging was available for 7 (58.3%) participants and included stage II [1 (8.3%) participant], IIIb [1 (8.3%) participant], IV [2 (16.7%) participants], and IVb [3 (25.0%) participants].

Regarding IDH gene mutation status, the most common IDH allele type was R132C, present in 11 (91.7%) participants, while 1 (8.3%) participant carried the R132G IDH allele type.

EXTENT OF EXPOSURE

Details on exposure to ivosidenib are provided in the safety results part of the synopsis.

EFFICACY RESULTS

- Primary efficacy endpoint

The primary objective of Study CL2-95031-008 was achieved, showing a statistically significant improvement in the PFS rate at 6 months by IRC assessment compared to the null hypothesis of a 6-month PFS rate ≤ 2.6% (1-sided p = 0.0032). The 6-month PFS rate by IRC assessment was 25% (90% CI: 8.1%, 46.5%).

Treatment effect durability was demonstrated, as 25% of participants treated with ivosidenib did not experience disease progression within 6 months. The median PFS was 2.7 months (95% CI: 1.48, 6.93). The 9-month PFS rate by IRC assessment was 16.7% (95% CI: 2.7%, 41.3%).

- Secondary efficacy endpoints

The 6-month PFS rate, as evaluated by the Investigator, was 33.3%, which was statistically significant (p=0.0002; 95% CI: 10.3, 58.8).

The high concordance rate of PFS and similar trends observed between the IRC and Investigator assessments reinforce the robustness and reliability of the study's findings.

The median PFS by Investigator assessment was 4.21 months (95% CI: 2.69, NE).

The KM analysis revealed that the PFS rates for participants at 3, 6, and 9 months were 66.7% (95% CI: 33.7, 86.0), 33.3% (95% CI: 10.3, 58.8), and 25.0% (95% CI: 6.0, 50.5), respectively.

The BOR indicated that most participants achieved SD, i.e., 8 (66.7%) per IRC and 11 (91.7%) per Investigator, suggesting that ivosidenib effectively stabilized the disease. Progressive disease was reported in 4 (33.3%) participants per IRC and 1 (8.3%) participant per Investigator.

No Participants achieved CR or PR.

DOR and TTR could not be analyzed.

Overall survival data for the ITT Set showed that 4 (33.3%) participants experienced an event of death, while 8 (66.7%) participants were censored (ongoing and alive) at the data cutoff date of 01 October 2024.

The HRQoL assessments using EORTC QLQ-C30 and EORTC QLQ-BIL21, and health economic assessments using EQ-5D-5L indicate that Japanese CCA participants maintained stabilized quality of life and functional status, with manageable symptoms of fatigue, pain, and biliary-related issues.

PK and PK/PD Results Summary

Ivosidenib was rapidly absorbed with median T_{max} at 2.98 hours following a single dose and at 3.83 hours following multiple doses. After single and multiple doses of ivosidenib at 500 mg, geometric mean plasma ivosidenib C_{max} was 4918 and 4781 ng/mL, respectively; geometric mean plasma ivosidenib [area under the plasma concentration-time curve (AUC)] AUC_{0-6} was 18699 and 22404 ng*h/mL, respectively; and geometric mean plasma ivosidenib AUC_{0-24} was 74121 ng*h/mL (C2D1 only). Mean accumulation ratios were 1.24 for AUC_{0-6} and 1.04 for maximum observed plasma concentration (C_{max}), respectively, suggesting low accumulation based on total exposure, occurred following 28 days of QD dosing. Plasma 2-HG concentrations were elevated at baseline and after a single 500 mg dose of ivosidenib, and mean 2-HG % inhibition based on $\%BAUEC_{0-6}$ was 34.7%. After a 28-day cycle of 500 mg QD dosing multiple doses of ivosidenib, the mean $\%BAUEC_{0-6}$ was 73.3%, and the mean plasma 2-HG concentrations decreased to levels observed in healthy participants (72.6±21.8 ng/mL). Plasma 2-HG levels remained similar to levels observed in healthy participants (72.6 ng/mL) with mean 2-HG Rtrough levels at C2D1 being 80.0 ng/mL. Ivosidenib mean plasma exposure as well as the effect of ivosidenib on 2-HG after multiple dose administration of ivosidenib 500 mg QD, were comparable between Asians and non-Asians from Study AG120-C-005 and the Japanese participants in this study.

SAFETY RESULTS

- **Extent of exposure**

The median duration of treatment was 5.1 months (range 1 to 10 months). All 12 participants (100.0%) were on treatment for ≥ 1 month. A total of 9 (75.0%) participants were on treatment for ≥ 3 months, 4 (33.3%) participants were on treatment for ≥ 6 months, and 2 (16.7%) participants were on treatment for ≥ 9 months.

The mean actual dose intensity was 478.5 mg/day (SD = 46.34), with a median of 500.0 mg/day (range 345 to 500 mg/day). The mean relative dose intensity was 95.7% (SD = 9.27), with a median of 100% (range: 69% to 100%), indicating excellent compliance with minimal dose modifications.

- **Action taken with study drug**

Overall, only 3 (25.0%) participants had at least one dose modification during the study. Among these, 2 (16.7%) participants experienced one dose interruption each, and 1 (8.3%) participant had a dose reduction due to an AE (QT prolongation) and 2 dose interruptions.

The data on maximum consecutive days of dose interruption duration showed that 3 (25%) participants experienced interruptions, with maximum duration of ≤ 28 days, with a mean duration of 9.7 days (SD = 3.21), and a median of 11 days (range 6 to 12 days).

- **Adverse events**

The treatment was generally well-tolerated, with most AEs reported as nonserious and Grades 1 and 2.

Of the 12 participants in the SAS, 9 (75%) participants experienced at least one TEAE. Three (25%) participants experienced Grade 3 or higher TEAEs: ECG QT prolonged reported in 2 (16.7%) participants and Lymphocyte count decreased reported in 1 (8.3%) participant. Among the participants, 8 (66.7%) participants had TEAEs that were related to the study drug, and 2 (16.7%) participants experienced ivosidenib-related TEAEs that were Grade 3 or higher (ECG QT prolonged).

Of the TEAEs experienced by the 9 (75.0%) participants, gastrointestinal disorders were common, affecting 3 (25%) participants, with diarrhea the most commonly reported AE within the System Organ Class (2 [16.7%] participants).

The most common TEAEs occurring in at least 10% of participants were prolonged ECG QT (25%), diarrhea (16.7%), and hypokalemia (16.7%).

Of the 12 participants, 2 (16.7%) experienced serious TEAEs of ECG QT prolongation, which were considered related to the study drug. One participant (8.3%) had a TEAE that led to an interruption of the study drug, and this event was also related to the study drug. Overall, while most participants experienced TEAEs, the majority of these events were of lower grade and did not result in significant modifications to the treatment regimen.

Of the 12 participants, ECG QT prolongation was the only AESI observed, affecting 3 (25%) participants. All 3 (25.0%) cases were considered related to the study drug; one leading to dose interruption and reduction, and none leading to treatment discontinuation.

- **Laboratory tests**

Most participants remained at their baseline toxicity grades. Minor shifts from baseline grades to Grade 1 or Grade 2 were observed.

The following summarizes the shifts from baseline to the worst post-baseline toxicity grades:

For ALT, 83.3% (10 of 12) of participants had a baseline Grade 0. Post-baseline, 75.0% of these participants remained at Grade 0, 8.3% shifted to Grade 1, and another 8.3% shifted to Grade 2.

For ALP, 25.0% (3 of 12) of participants with a baseline Grade 0 remained at Grade 0. Additionally, 33.3% (4 of 12) of participants with a baseline Grade 1 and 25.0% (3 of 12) of participants with a baseline Grade 2 improved to Grade 0. Only 16.7% of participants progressed from Grade 0 to Grade 1, and no participants progressed to Grade 2, 3, or 4.

For AST, overall, 33.3% (4 of 12) of participants retained their baseline grade at Grade 0, and 50% (6 of 12) participants improved from Grade 1 to Grade 0. Only 16.7% participants progressed from Grade 0 to Grade 1. No participants progressed to Grades 2, 3, or 4.

For serum potassium (low), 75.0% (9 of 12) of participants had a baseline Grade 0. Post-baseline, 16.7% of these participants shifted to Grade 2. Additionally, one participant (8.3%) participant who initially exhibited Grade 2 remained at that toxicity level.

For serum potassium (high), 75.0% (9 of 12) of participants remained at a baseline Grade 0 post-baseline, while 25.0% shifted to Grade 1.

For serum bilirubin (high), 91.7% (11 of 12) of participants remained at a baseline Grade 0 post-baseline, and 1 (8.3%) participant with a baseline Grade 1 improved to Grade 0

For serum sodium (low), 50.0% (6 of 12) of participants maintained a baseline Grade 0, 25.0% shifted to Grade 1, and 25.0% with a baseline Grade 1 remained at that level post-baseline.

For hemoglobin (low), most participants with baseline Grade 0 or 1 experienced slight shifts. Specifically, 3 (25%) participants shifted from Grade 0 to Grade 1 and 3 (25%) participants from Grade 1 to Grade 2. Only 1 participant (8.3%) reached Grade 3.

Neutrophil levels (low) remained largely stable, with 11 (91.7%) participants maintaining a Grade 0 and 1 (8.3%) participant shifting to Grade 2.

Leukocyte count (low) showed minimal changes, with 11 (91.7%) participants retaining their Grade 0 status and only 1 (8.3%) participant shifting to Grade 3. No participants exhibited high leukocyte levels post-baseline.

For those with initial Grade 0 platelet levels (low), 6 (50%) participants remained at Grade 0, while 1 (8.3%) participant shifted to Grade 1. Among those with initial Grade 1 levels, 1 (8.3%) participant improved to Grade 0 and 4 (33.3%) participants remained at Grade 1, maintaining mild toxicity. There were no participants whose platelet levels worsened to Grades 2, 3, or 4.

Baseline coagulation profiles were mostly normal with minor deviations; however, these fluctuations were not clinically significant.

Urinalysis did not reveal any clinically significant findings.

No pregnancies were reported in the study.

Other tolerance criteria (vital signs, ECG etc)

Overall, vital signs were within normal values. The only vital signs abnormalities reported as AEs (Grade 1) were pyrexia and weight decreased, each reported in 1 (8.3%) participant.

The study drug had no significant impact on QTcF or RR intervals, indicating stable cardiac function.

Most participants maintained stable physical activity levels. At the worst post-baseline assessment, 7 (58.3%) remained fully active, 4 (33.3%) had slight restrictions, and 1 (8.3%) experienced a moderate decline (ECOG 2).

Most participants (11 out of 12) had normal LVEF (63%-69%), indicating normal cardiac function before treatment. One participant had a slightly reduced LVEF of 58% that was not clinically significant.

Based on these findings, ivosidenib was well tolerated.

CONCLUSION

Ivosidenib demonstrated potential in stabilizing disease in Japanese patients with IDH1-mutated CCA, showing a PFS benefit that is clinically meaningful for this rapidly progressive disease. This study met its primary endpoint. Progress-free survival at 6 months by IRC achieved statistical significance (6-month PFS rate by IRC: 25% [90% CI: 8.1%, 46.5%], 1-sided p-value: 0.0032). Ivosidenib's benefit was primarily through disease stabilization, and the impact on objective response rates was limited. The majority of participants remained alive at the time of the data cut-off, with OS data suggesting some initial survival benefits. The PK profile showed acceptable plasma concentration-time profiles and relevant PK parameters, and the PD relationship between ivosidenib and 2-HG levels was well-characterized, without any substantial differences noted between the Japanese population and participants from Study AG120-C-005 (CLARIDHY). The treatment was well-tolerated, with manageable side effects and stabilization of quality-of-life measures. These findings indicate that ivosidenib is a safe and effective targeted therapy for managing IDH1-mutated CCA in Japanese participants, with a similar benefit-risk profile as demonstrated previously in the overseas Phase 3 ClarIDHy study.

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