INSTITUT DE RECHERCHES INTERNATIONALES SERVIER (I.R.I.S.)

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Document title	**STATISTICAL ANALYSIS PLAN (SAP)**
Full title	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
Test drug code	S095031 (formerly known as AG-120)
Test drug name(s)	Ivosidenib
Indication	Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation
Development phase	Phase II
Sponsor	Institut de Recherches Internationales Servier (I.R.I.S.)
Regulatory agency identifier number(s) and/or public registration number(s)	NCT06081829
Date of the document	19 March 2024
Version of the document	Final version 1.0

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Follow up of versions

Version	Release date (dd/mm/yyyy)	Key change(s) (*)	Protocol version associated	Rationale
1.0	8/3/2024	Not applicable	1.0 Non-substantial amendment no.1, no.2 and no.3	Not applicable

(*) Key changes as compared to the statistical analyses planned in the protocol for the first SAP signed version (1.0). Key changes from the previous signed version for the other SAP signed version(s). See also section 7 for the changes to protocol-planned analyses.

CL2-95031-008 - Statistical Analysis Plan | VV-TMF-169574 | 1.0

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AE	:	Adverse event
ALP	:	Alkaline phosphatase
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
BOR	:	Best overall response
BUN	:	Blood urea nitrogen
C1D1	:	Cycle 1, Day 1
CR	:	Complete response
CSP	:	Clinical study protocol
CTCAE	:	Common Terminology Criteria for Adverse Events
DOR	:	Duration of response
ECOG	:	Eastern Cooperative Oncology Group
EORTC	:	European Organisation for Research and Treatment of Cancer
EOT	:	End of treatment
HRQOL	:	Health-related quality of life
IDH	:	Isocitrate dehydrogenase protein
IRC	:	Independent Radiology Center
ITT	:	Intent-to-Treat
LDH	:	Lactate dehydrogenase
LVEF	:	Left ventricular ejection fraction
NCI	:	National Cancer Institute
OR	:	Objective response
OS	:	Overall survival
PAS	:	Pharmacokinetic Analysis Set
PD	:	Progressive disease
PFS	:	Progression-free survival
PK	:	Pharmacokinetic
PPS	:	Per-Protocol Set
PR	:	Partial response
PT	:	Preferred Term, Preferred Term
QD	:	Once daily
QLQ-BIL21	:	Quality Of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer Module
QLQ-C30	:	Quality of Life Questionnaire - Core Questionnaire
RBC	:	Red blood cell
RECIST	:	Response Evaluation Criteria in Solid Tumors
SAE	:	Serious adverse event
SAS	:	Safety Analysis Set
SD	:	Standard deviation, Stable disease
SMQ	:	Standardized MedDRA Query
SOC	:	System Organ Class, System Organ Class
TEAE	:	Treatment-emergent adverse event
TLG	:	Tables, Listings and Graphs
TTR	:	Time to response
ULN	:	Upper limit of normal
WBC	:	White blood cell

1. INTRODUCTION

This Statistical Analysis Plan details the planned analyses to be performed, in accordance with the main characteristics of the study protocol version 1.0 dated from 20/03/2023, non-substantial protocol amendment 1 dated from 24/05/2023, non-substantial protocol amendment 2 dated from 29/06/2023 and non-substantial protocol amendment 3 dated from 13/02/2024. The primary analyses will be performed approximately 6 months after the last subject enrolled for the 6-month PFS rate assessment. The additional analyses will be performed at the end of the study.

The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

1.1. Study objectives and endpoints

Objective	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, AEs leading to discontinuation or death. The severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v 5.0. – Safety laboratory parameters, vital signs, 12-lead 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), duration of response (DoR), and time to response (TTR), with response assessed per Investigator and by the IRC.	– OS, defined as the time from Day 1 (C1D1) to date of death due to any cause. – 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 occurs first. – OR, defined as objective response (confirmed CR or confirmed 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 complete response (CR) or confirmed partial response (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. – PFS as determined by the Investigator.
To evaluate health-related quality of life (HRQOL) with ivosidenib	– HRQOL as assessed by validated instruments (EORTC-QLQ-C30, EORTC-QLQ-BIL21).

Objective	Endpoints
	– 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-HG in blood samples	– Blood sampling at specified time points for determination of 2-HG levels to characterize the PD effects of ivosidenib.

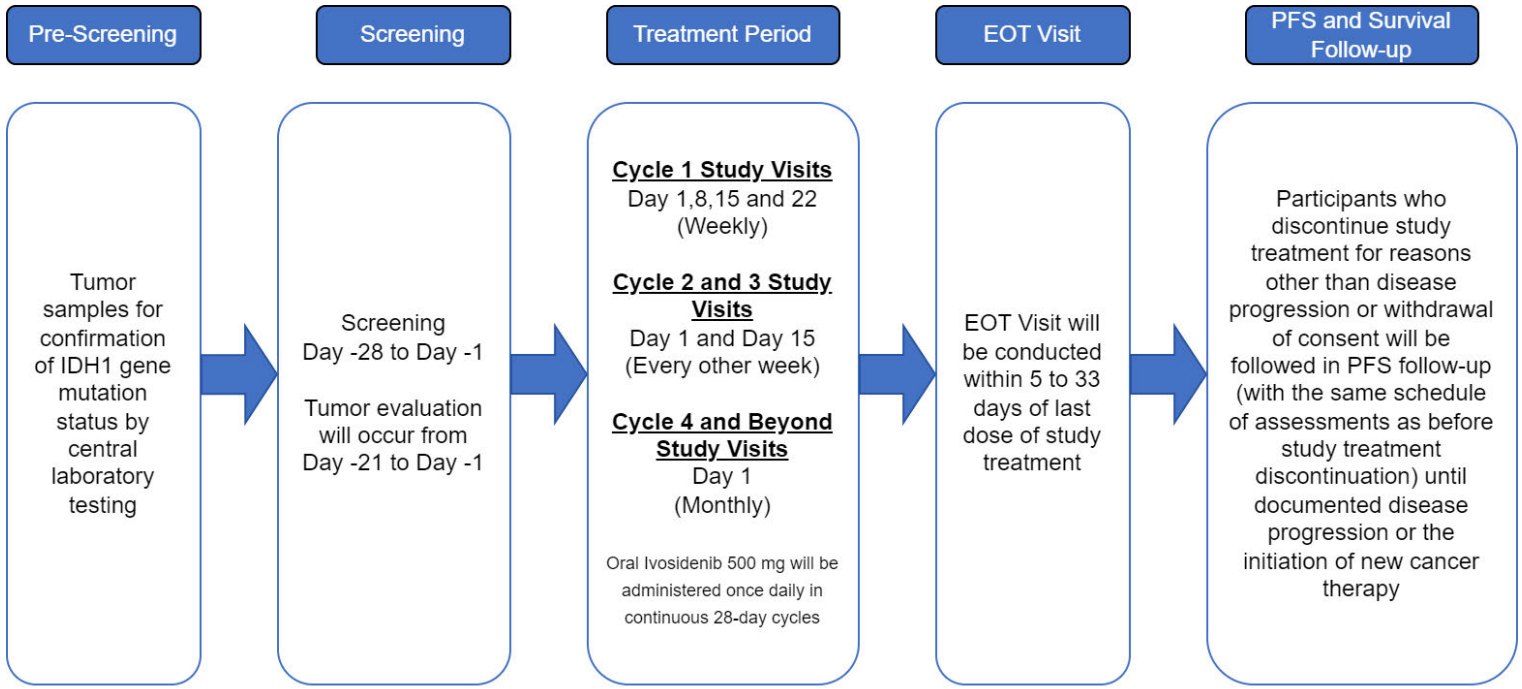
1.2. Study design

This is an open-label, single arm, multicenter study of orally administered ivosidenib in Japanese subjects with previously treated IDH1 gene-mutated cholangiocarcinoma.

1.2.1. Study plan

The overall study plan is demonstrated in Figure (1.2.1) 1. Subjects will continue to receive study treatment until disease progression unless discontinued due to other reasons. Subjects who discontinued treatment for reasons other than disease progression or withdrawal of consent will be followed in PFS follow-up with the same schedule of assessments as before study treatment discontinuation, until documented disease progression the initiation of new anti-cancer therapy, death. withdrawal of consent, or the end of study/study termination, whichever occurs first. OS follow-up assessments will occur approximately every 12 weeks after EOT unless the participant is in PFS follow-up at that time. OS follow-up will continue until all participants have died, withdrawn consent, or are lost to follow-up, or up to 24 months after the last participant enrolled, whichever comes first. Final analysis for OS will be conducted at the end of the study For the details on study design and measurements to be collected in each period, refer to the Section 4.4.1 of the clinical study protocol (CSP).

Figure (1.2.1) 1 Study plan



If a participant progresses or does not come back for scans while in PFS follow-up, then the OS follow-up assessments will begin at the next planned OS follow-up time point, following the schedule of every 12 weeks.

1.2.2. Type of randomization

Randomization is not applicable in this single arm, open-label study.

1.3. Determination of sample size

Approximately 10 Japanese subjects will be enrolled in the study.

The primary endpoint is PFS status (as assessed by IRC per RECIST v1.1) at 6 months after Day 1 (C1D1). Assuming a target 6-month PFS rate of 32% and a dropout rate of 10%, the study needs to enroll 10 subjects to provide approximately 84% power to reject the null hypothesis of PFS rate ≤ 2.6% using exact binomial test at 1-sided significance level of 0.05.

2. STATISTICAL HYPOTHESES AND MULTIPLICITY HANDLING

2.1. Statistical hypothesis

The following hypothesis test will be conducted using exact binomial test with 1-sided significance level of 0.05 for the primary endpoint (see Section 5.3.1):

- H_0 (null hypotheses): $\Phi_1 \leq 2.6\%$
- H_1 (alternative hypotheses): $\Phi_1 > 2.6\%$
- Φ_1 is the 6-month PFS rate

2.2. Multiplicity handling

Not applicable.

3. ANALYSIS SETS

3.1. Analysis sets

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

- Intent-to-Treat Analysis Set (ITT): All subjects who were included and treated. The ITT will be used for the primary efficacy analyses and is the default analysis set unless otherwise specified.
- Safety Analysis Set (SAS): All subjects who received at least one dose of study treatment. The SAS will be the primary set for the analysis of safety data, unless otherwise specified.
- Per-Protocol Set (PPS): All subjects in the ITT who do not violate the terms of the protocol in a way that would affect the study outcome significantly. The PPS will be used to perform sensitivity analyses for the primary endpoint. In general, subjects who meet the following criteria will be excluded from this analysis set:
  - Do not have histopathologically diagnosed nonresectable or metastatic cholangiocarcinoma.
  - Do not have documented IDH1 gene-mutated disease based on central laboratory testing.
  - Do not have any measurable lesion at baseline as defined by RECIST v1.1 as determined by IRC or by Investigator.
  - Three or more prior systemic therapy in an advanced setting (nonresectable or metastatic)
  - Have received a prior IDH inhibitor.
- Pharmacokinetic Analysis Set (PAS): All subjects who have at least 1 blood sample post-dose providing evaluable PK data for ivosidenib.
- Pharmacodynamic Analysis Set: All participants who have had at least one blood sample providing evaluable plasma 2-HG data for ivosidenib.

3.2. Treatment groups

All subjects enrolled will be administered the study drug orally at a dose of 500 mg (provided as 250 mg strength tablets).

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. Descriptive statistics

Summaries will be produced for disposition, demographic and baseline disease characteristics and efficacy variables, as appropriate.

For qualitative data, number of observed values, number, and percentage of subjects per class will be presented. Unless otherwise specified in the TLG, no class "Missing" is considered.

For quantitative data, number of observed values, mean, standard deviation (SD), median, first and third quartiles, minimum and maximum will be presented. The geometric mean will also be provided for log-distributed data (if applicable).

Time-to-event endpoints will be estimated using Kaplan-Meier methods. Point estimates and 95% CIs will be provided where appropriate, and estimates of the median and other quantiles, as well as individual time points (e.g., 3-month, 6month, and 12-month rates) will be produced.

5. STATISTICAL ANALYSES

5.1. Study Subject

5.1.1. Disposition

The number (%) of subjects included in each of the analysis populations listed in Section 3.1 will be summarized.

The number (%) of subjects in the following categories will be provided for all subjects enrolled:

- Enrolled and treated subjects.
- Enrolled and not treated subjects.
- Subjects still on treatment.
- Subjects who discontinued the treatment and the primary reason for treatment discontinuation.
- Subjects still on PFS follow-up.
- Subjects still on OS follow-up.
- Subjects still on study.
- Subjects who did not complete the study as per protocol and the primary reason for study discontinuation.

5.1.2. Important Protocol deviations (IPD)

IPD will be summarized in the ITT set including the following categories:

- Number and percentage of subjects with at least 1 IPD.
- Subjects by number of IPDs (1, 2, ≥3).
- Number and percentage of subjects within each IPD category.

5.1.3. Demographic data and baseline characteristics

Demographic and other baseline variables will be descriptively summarized on ITT set.

5.1.3.1. Demographics and Physical Measurements

- Gender (Female, Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Island, White, Unknown, Not Reported)
- Age (years)
- Age group (<45, ⩾45 -<65, ⩾65 years)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino, Unknown, Not Reported)
- Height (cm)
- Weight (kg)
- Body mass index (BMI, kg/m2)

If age is not collected in the database, it will be calculated as follows: age = [ICF year – birth year].

5.1.3.2. Baseline disease and other characteristics

The following baseline characteristics will be summarized based on ITT set:
- IDH1 allele types per central IDH1 testing.
- ECOG at baseline.
- Cholangiocarcinoma type at diagnosis (Intrahepatic Cholangiocarcinoma, Distal Cholangiocarcinoma, Perihilar Cholangiocarcinoma, Unknown Cholangiocarcinoma).
- T/N/M (Tx, Nx, Mx) or Staging (I to IVc) Cholangiocarcinoma at initial diagnosis.
- Extent of disease at Screening (Local/regional, Metastatic).
- Presence of Liver cirrhosis at Screening.
- Biliary drainage/stent related to Cholangiocarcinoma within the past 3 months.
- Presence of Ascites at Screening.
- Ascites related to Cholangiocarcinoma within the past 3 months.
- Paracentesis within the past 3 months.
- Pleural effusion related to Cholangiocarcinoma within the past 3 months.
- Thoracentesis within the past 3 months.

Data on disease characteristics will be provided in by-subject listing.

5.1.3.3. Medical and surgical history

Medical and surgical history includes all the relevant medical and surgical history during the lifetime of the subject. Medical and surgical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) on ITT set.

A listing of medical history will also be provided.

5.2. Treatments of subjects

5.2.1. Extent of exposure and treatment compliance

Extent of exposure will be summarized on the SAS by the following variables:
- Duration of treatment (in months): (Date of the last dose – Date of the first dose + 1)/30.4375
  - For subjects who are still on treatment at a data cut-off date, the data cut-off date will be the date of the last dose.
  - Duration of treatment will be summarized continuously and categorically (e.g. <1, ⩾1, ⩾3, ⩾6, ⩾9, ⩾12 months).
- Actual Dose Intensity (mg/day): Actual total dose/duration of treatment (days).
- Relative Dose Intensity (%): Actual dose intensity/planned dose intensity, where the planned total daily dose is the dose assigned at the study entry.
- Dose modification (dose reduction, dose interruption) and the reasons for dose modifications.

5.2.2. Prior and Concomitant therapies

5.2.2.1. Prior systemic anticancer therapy

Prior therapies will be summarized on the ITT set. Types of therapies (adjuvant, palliative, etc.) will also be summarized.

Duration of last line of therapy (in months) in advanced setting will be summarized, calculated as (end date of the last line of therapy – start date of the last line of therapy + 1)/(30.4375).

In case there are multiple drugs within 1 line of therapy, the outer window rule will be applied to calculate the duration: the earliest start date of all drugs will be the start date, and the latest end date will be the end date for that line. A data listing will be provided and the line that is contributed to the eligibility will be flagged.

5.2.2.2. Prior Local-Regional Therapy

Prior local or regional therapies will be summarized on ITT set.

A data listing will be provided for prior local-regional therapy, including the type of prior local regional therapy, anatomical location, start date, end date, therapy setting, best response, and date of progression.

5.2.2.3. Prior Surgery for Cholangiocarcinoma

Prior surgery for cholangiocarcinoma will be summarized on ITT set.

A data listing will be provided for prior surgery, including procedure, location, date of procedure, whether disease recur or progress after the procedure, and date of recurrence or progression.

5.2.2.4. Prior and concomitant medications/procedures

Prior and concomitant medications, and concomitant procedures will be summarized on ITT set.

Prior medications are those the subject received prior to first study drug administration. Prior medications can be discontinued before first administration or can be ongoing during treatment period.

Concomitant medications and concomitant procedures are defined as ongoing at the time of first study drug administration or that were initiated after the first dose but prior to the last dose plus 28 days (inclusive). If an end date is missing or the medication/procedure is ongoing, the medication/procedure will be included as concomitant medication/procedure.

A given medication can be classified as a prior medication and/or as a concomitant medication. If it cannot be determined whether a given medication was taken prior or concomitantly, it will be considered as prior and concomitant medication. Concomitant procedures can be classified by the similar rule as concomitant medication.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the latest version and will be tabulated by anatomic therapeutic class (ATC) in 4 levels (pharmacological class, pharmacological sub-class, therapeutic class, Preferred name).

In addition, the following data listings will be provided:

- A listing for prior and concomitant medications, with a flag to indicate prior vs. concomitant.
- A listing of concomitant procedures.

5.3. Efficacy analyses

Response to treatment will be assessed by the site Investigators and by the IRC using RECIST v1.1.

5.3.1. Primary efficacy endpoint

The primary analysis will be performed on the ITT set.

The progression-free survival (PFS) by IRC is defined as the time in months from Day 1 (C1D1) to the date of the first documentation of disease progression as determined by the IRC per RECIST v1.1 or death due to any cause, whichever occurs first.

PFS = (Earliest Date of Disease Progression or Death – Day 1 Date + 1) / 30.4375.

The primary endpoint is PFS status at 6 months after Day 1 (C1D1). The 6-month PFS rate defined as the probability of subjects who are alive and progression-free at 6 months after Day 1 (C1D1) will be used to assess the primary endpoint. Kaplan-Meier method will be used to estimate the 6-month PFS rate. Exact binomial test with 1-sided significance level of 0.05 will be used to compare the 6-month PFS rate against 2.6%.

Subjects without documentation of disease progression or death at the time of the analysis of PFS will be censored at the date of the last response assessment prior to the start of alternate therapy. See Table (5.3.1) 1 for the details on handling of missing response assessments and censoring.

Number of subjects with events, types of events (progression or death), and number of subjects censored, number of subjects for each reason of censoring, Kaplan-Meier estimates, and 95% CIs according to Brookmeyer and Crowley method for the median, Q1 and Q3 for PFS will be presented. Probabilities of event free at selected time points, such as 3-month, 6-month, 9-month, and 12-month, will be presented. Kaplan-Meier curves of PFS will be provided with the number of subjects at risk over time included.

In addition, the concordance of PFS between investigator and IRC assessment will also be summarized.

Table (5.3.1) 1 Handling of Missing Response Assessment and Censoring for the Primary Analysis of PFS

Situation	Date of Censoring
No baseline assessment and no death.	Date of the Cycle 1 Day 1
Alternate anticancer systemic treatment started before documented progression (PD) per RECIST 1.1 or death.	Date of last adequate assessment prior to the start of alternate anticancer treatment[1]
No adequate post-baseline assessment and no death.	Date of the Cycle 1 Day 1
No documented PD per RECIST 1.1 or death before data cut-off date or before permanently discontinued from the study.	Date of last adequate assessment[1]

Situation	Date of Censoring
Documented PD per RECIST 1.1 or death following a long gap from the previous adequate assessment (e.g., 2 or more consecutive missed scheduled disease status assessments). The long gap is defined as ⩾95 days (ie, 12 weeks + 10 days per the protocol defined visit window). If no adequate assessment prior to minimum of (PD, death), the long gap is calculated from the Cycle 1 Day 1.	Date of last adequate assessment prior to the first occurrence of 2 or more consecutive missing scheduled assessments

[1] Adequate disease assessment is defined as a response assessment other than "not evaluable." If there is no adequate response assessment prior to the start of anticancer treatment, it will be censored at the date of Cycle 1 Day 1.

5.3.1.1. Sensitivity analysis

The primary efficacy endpoint may be analyzed based on the PPS using the same method in the primary analysis.

5.3.2. Secondary efficacy endpoints

5.3.2.1. Overall survival (OS)

Overall survival is defined as the time from C1D1 to the date of death due to any cause. Subjects will be followed for survival until all subjects have either died, withdrawn consent, are lost to follow-up, or up to 24 months after last subject enrolled, whichever occurs first. Subjects who are alive at the analysis cutoff date will be censored at the date of last contact.

Kaplan-Meier estimates of OS will be presented, including estimates of the median and other quantiles, as well as individual time points (e.g., 3-month, 6-month, and 12-month rates).

Duration of follow-up defined as the time from C1D1 to the earliest of last known alive date or data cutoff date will also be analyzed in the same way as OS. Subjects with documentation of death on or before the time of data cutoff will be censored at the date of death.

5.3.2.2. PFS per investigator

PFS per investigator is defined as the time from C1D1 to the date of first documentation of disease progression as assessed by investigator per RECIST v1.1 or death due to any cause, whichever occurs first.

The same censoring rules as the primary endpoint of PFS will be applied to PFS per Investigator.

The analysis for PFS per investigator will be like PFS by IRC (see Section 5.3.1).

5.3.2.3. Objective response (OR)

Objective response is defined as confirmed CR or PR per RECIST v1.1. OR will be analysed by IRC as primary analysis and by Investigator as sensitivity analysis.

Objective response rate (ORR) will be derived from the best overall response (BOR). BOR is defined as the best time point response that a subject achieves during the course of the study, with the response ranked according to the following order (from best to worst): CR>PR>SD>PD>UNK>Other (including Not Evaluable and Not Assessed). The number and proportion of subjects by category of BOR will be presented. The number and proportion (95% CI based on Clopper-Pearson method) of subjects who achieved OR will be presented. If the subject has no response assessment, it will be treated as a non-responder in the analyses.

Per RECIST v1.1, SD that occurred within <38 days from C1D1 is assigned as UNK (6 weeks minus 5 days per protocol allowed visit window). In addition, the BOR of CR or PR requires a confirmation scan. The specific confirmation rule can be found in Table 3 of CSP.

The waterfall plot of the best % change from baseline in target lesion measurement (sum of diameters) will be presented. The target lesions post-baseline vs. baseline have to be matched in order to calculate % change, except for the case where lesions disappeared (Absent or Too Small to Measure) or merged or split. If the lesion status is “Absent,” 0 mm will be used as the measurement; if the lesion status is “too small to measure,” 5 mm will be used per RECIST v1.1 guidance.

The swim lane plot of treatment duration per subject will be presented. Treatment ongoing status will be marked at the end of the lane. The BOR will be marked in colors. The swim lane plot will be based on ITT set.

A summary of best overall response will be listed.

5.3.2.4. Duration of response (DoR)

A responder is defined as a subject who achieved objective response (see Section 5.3.2.3). Among the responders, DoR in months will be calculated from the date of the first occurrence of response to the date of first documented disease progression or death, whichever comes earlier. See Table (5.3.1) 1 for the censoring rules.

Duration of response = (Earliest Date of Death/Progression – Date of First Confirmed PR/CR + 1)/30.4375.

DoR may be analysed by IRC as primary analysis and by Investigator as sensitivity analysis. If there are at least 5 responders, Kaplan-Meier plot of DoR may be generated.

Listing on DoR will be provided for responders.

5.3.2.5. Time to response (TTR)

Time to response is defined as the time (in months) from the C1D1 to the date of first occurrence of confirmed response per RECIST v1.1. TTR may be analysed by IRC as primary analysis and by Investigator as sensitivity analysis.

Time to response = (Date of First Confirmed PR/CR – Day 1 Date + 1)/30.4375.

Listing on TTR will be provided for responders.

5.4. Safety analysis

Unless specified otherwise, all safety analyses will be performed on the SAS as defined in Section 3.1. The analysis of the safety data will be descriptive, and no testing is planned.

5.4.1. Adverse events

Treatment-emergent adverse event (TEAE) is defined as adverse events that take place between the first study drug intake date (inclusive) and last study drug intake date +28 days (inclusive). TEAE will be summarized according to Medical Dictionary for Regulatory Activities (MedDRA) by SOC and/or PT, severity (based on NCI CTCAE v 5.0 grading as assessed by the Investigator), seriousness, and relation to study drug.

If the assessment of the relationship to study drug is missing for an AE, this AE will be assumed as related to study drug. Missing grade will be left as missing.

Multiple occurrences of the same event in the same subject will be counted only once in the tables within treatment-emergent period using the worst (maximum value) grade. Summaries will be provided for all grades combined and for grade ≥3. Missing grades, if any, will be included in the "all grades" category.

The AE tables will be sorted as indicated in Table (5.4.1) 2.

Table (5.4.1) 2 – Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the alphabetical SOC order and decreasing frequency of PTs
SOC	By the alphabetical SOC order
PT	By decreasing frequency of PTs

Analysis of all adverse events

The overview of TEAE in the below categories will be generated:

- TEAE.
- TEAE leading to dose modification (interruption / reduction).
- TEAE related to study drug.
- TEAE leading to study drug withdrawal.
- TEAE related to study drug leading to dose modification.
- TEAE related to study drug leading to study drug withdrawal.
- Grade ≥3 TEAE.
- Grade ≥3 TEAE related to study drug.
- Common TEAE (≥10% in all subjects).
- Grade ≥3 Common TEAE (≥10% in all subjects).
- Grade ≥3 Common TEAE (≥10% in all subjects) related to study drug.
- Treatment-emergent serious AE.
- Treatment-emergent serious AE related to study drug.
- Treatment-emergent fatal AE.
- Treatment-emergent fatal AE related to study drug.

- The AE summaries of Table (5.4.1) 3 will be generated with number (%) of subjects experiencing at least one event.

Table (5.4.1) 3 – MedDRA levels of adverse events

Type of AE	MedDRA levels
TEAE	SOC and PT
	SOC
	PT
TEAE leading to dose modification (interruption / reduction)	SOC and PT
TEAE related to study drug	SOC and PT
TEAE leading to study drug discontinuation	SOC and PT
TEAE related to study drug leading to study drug discontinuation	SOC and PT
Grade ≥3 TEAE	SOC and PT
Grade ≥3 TEAE related to study drug	SOC and PT
Common TEAE (≥10% in all subjects)	PT
Treatment-emergent SAE	SOC and PT
Treatment-emergent SAE related to study drug	SOC and PT
Treatment-emergent fatal AE	SOC and PT

The overview of treatment duration adjusted incidence rate of TEAE for subjects with an event per person-year will also be generated.

All AEs will be listed by subjects and TEAE will be flagged in the listings.

Analysis of adverse events of special interest (AESIs)

QT prolongation event using the search criterion of SMQ (Broad) of Torsade de pointes/QT prolongation will be selected.

The AESI will be summarized for the following:
- Any grades by PT.
- Grade ≥3 by PT.
- Any grades related to study drug by PT.

Time to onset of the AESI event will be summarized quantitatively and categorically by ≤15 days, 16-30, 31-45, 46-60, and >60 days for all grade and Grade 2 or higher AEs.

Analysis of deaths

On-treatment deaths (within the 28 days after last dose of study drug) and all deaths with the reasons of deaths will be summarized. Listing of individual subjects will be provided.

In addition, all-cause mortality will be summarized including the deaths ≤30 days of the first and last dose, and ≤60 days of the first and last dose.

5.4.2. Clinical laboratory evaluation

The hematology and chemistry parameters will be presented in both actual values and changes from baseline as appropriate by scheduled visits. Coagulation, urinalysis and pregnancy test results will be presented in listings. They will be converted into standard international units.

- Hematology
  - Hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils count, lymphocytes count and differential (% neutrophils, % bands), platelet count.
- Serum chemistry
  - Sodium, potassium, total calcium, magnesium, phosphate, albumin, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin.
- Coagulation Studies
  - Prothrombin time (PT) and/or international normalized ratio (INR), activated partial thromboplastin time (aPTT).
- Urinalysis
  - Color and appearance; pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood; and microscopic inspection of sediment.
- Pregnancy Test
  - For female subject, a serum pregnancy test will be performed at Screening; a serum or urine pregnancy test must be conducted and confirmed negative on the first day of study drug administration before dosing and on Day 1 of every cycle.

Shift tables from baseline to worst value based on CTCAE V5.0 grade will be presented, including:

- White blood cell (low).
- Absolute neutrophil count (low).
- Hemoglobin (low).
- Platelet count (low).
- Total Bilirubin (high).
- Alkaline Phosphatase (high).
- ALT (high).
- AST (high).
- Sodium (low).
- Potassium (low/high).
- Phosphate (low).

In addition, subjects with liver dysfunction will be presented in a listing. Liver dysfunction is defined as elevated ALT or AST of ≥ 3x ULN and associated with increase in total bilirubin ≥2x ULN (±10 days).

5.4.3. Vital signs, clinical examination and other observations related to safety

5.4.3.1. Vital signs and clinical examination

Vital signs (except height) will be presented as both actual values and changes from baseline by scheduled visits. Vital sign measurements will also be listed.

5.4.3.2. Electrocardiogram

Descriptive statistics for the actual values and changes from baseline over time will be summarized for each ECG parameter: QT (msec), RR interval (msec) and QTcF (Fridericia's correction). QTcF is calculated as QTcF = QT/cube root of RR interval.

The proportion of subjects with maximum post-baseline absolute QTcF intervals that fall into following categories will be presented:

- ≤450 msec.
- >450 and ≤480 msec.
- >480 to ≤500 msec.
- >500 msec.

The proportion of subjects who have a maximum post-baseline change from baseline in QTcF intervals of the following categories will be presented:

- ≤0 msec.
- >0 to ≤30 msec.
- >30 to ≤60 msec.
- >60 msec.

A listing of subject-level ECG measurement will be provided.

5.4.3.3. Left Ventricular Ejection Fraction (LVEF)

The LVEF data will be listed.

5.4.3.4. ECOG Performance Status (PS)

The ECOG PS will be summarized by visit, and by shift tables from baseline to worst values across all visits.

A by-subject listing will be provided.

5.5. Quality of Life

In general, descriptive statistics will be used to summarize the individual items and sub-scale scores of HRQOL (EORTC-QLQ-C30, and EORTC-QLQ-BIL21) and EQ-5D-5L data at each scheduled assessment time point. Data listings will also be provided by each endpoint and visit for each subject.

5.5.1. EORTC-QLQ-C30

The QLQ-C30 is a cancer specific instrument that contains 30 questions and provides a multi-dimensional assessment of health related QoL. The QLQ-C30 incorporates five functional scales (Physical functioning, Role functioning, Cognitive functioning, Emotional functioning and Social functioning), three symptom scales (Fatigue, Pain and Nausea/Vomiting), six additional single items (Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea and Financial Difficulties) and a global health status (GHS) as symptoms commonly reported by cancer patients and the perceived financial impact of the disease.

The raw scores are linearly transformed to scale scores in the range of 0-100 based on EORTC guidelines. Higher scores in the global and functioning scales and lower scores in the symptom/single scales indicate better quality of life. See Appendix C for the calculation of raw score and transformed scale score.

Transformed scores for each scale and the absolute change from baseline will be summarized by visit.

5.5.2. EORTC-QLQ-BIL21

The QLQ-BIL21 is for assessing the QoL in subjects with cholangiocarcinoma, it consists of five scales and three single items,

- 5 scales (18 items): eating symptoms (4 items), jaundice symptoms (3 items), tiredness (3 items), pain symptoms (4 items), anxiety symptoms (4 items).
- 3 single-item assessments related to treatment side-effects, difficulties with drainage bag/tubes, concerns regarding weight loss.

Similar to QLQ-C30, QLQ-BIL21 scores will be transformed to scale scores as well and will be summarized by visit.

5.5.3. EQ-5D-5L

The EQ-5D-5L incorporates the EQ-5D descriptive system and a visual analogue scale (VAS).

The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. For each dimension, the number and percentage of subjects in each category will be summarized by visit.

The EQ VAS records the respondent's self-rated health ranging between 0 (worst health) and 100 (best health). Summary statistics for VAS score and the absolute change from baseline will be reported by visit.

5.6. PK and PK/PD analyses

PK-related analyses on Pharmacokinetic Analysis Set (PAS) and Pharmacodynamic Analysis Set will be documented and reported separately.

5.7. Exploratory analysis

Not applicable.

5.8. Biomarkers analysis

Analyses for PD biomarkers will be documented and reported separately.

6. INTERIM ANALYSIS

Not applicable.

7. CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

8. APPENDICES

8.1. Appendix A: Data handling conventions

8.1.1. General conventions

Summary statistics will be presented by treatment and scheduled visit, unless stated otherwise. Unless otherwise specified, descriptive statistics for continuous data will include the number of subjects with data to be summarized (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects will be used as the denominator for percent calculations, unless stated otherwise.

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

Listings will be provided for selected endpoints. Listings will be sorted by site, treatment, and subject IDs.

8.1.2. Relative study days

All data listings that contain an evaluation date will contain a relative study day.

Study days are numbered relative to C1D1 starting from Day 1 for all outputs. The preceding day is Day −1, the day before that is Day −2, etc. There is no Day 0.

8.1.3. Baseline values

Unless otherwise specified, the baseline value is defined as the latest value prior to the start of study drug administration. In case subjects are not exposed, the latest assessment will be considered as baseline. Values collected at unscheduled visits prior to the start of the study drug administration will be included in the calculation of baseline values. In majority of cases, C1D1 assessment should be treated as the baseline as the study protocol requires assessment to be done pre-dose at C1D1.

8.1.4. Unscheduled Visits and Visit Windows

Unscheduled visits will not be mapped and will not be included in the summary statistics per visit tables. However, they will be included in the data listing as well as the shift tables.

8.2. Appendix B: Handling of missing data

8.2.1. Missing data handling for efficacy data

Refer to Table (5.3.1) 1 for missing response assessment and censoring rules.

8.2.1.1. Missing/Partial Dates in On-study Anticancer Therapies

On-study anticancer therapy with start dates that are completely or partially missing will be imputed as follows:

1. If the start date has month and year but day is missing, the 15 of the month will be used.
2. If the start date has year, but day and month are missing, July 1 will be used.

On-study anticancer therapy with stop dates that are completely or partially missing will be imputed as follows:

1. If the stop date has month and year but day is missing, the last day of the month will be assigned.
2. If the stop date has year, but day and month are missing, December 31 will be assigned.
3. If the stop date misses day, month and year, the event will be considered as ongoing.

If the imputed date is before the last dosing date, the last dosing date will be used as the on-study anticancer therapy start date. If the imputed date is after the death date, then the death date will be used. If the imputed stop date is before start date, the stop date will be used as the start date.

This imputation rule will only be used in efficacy endpoints derivation (such as PFS, OS). The listing of post-study anticancer therapy will not apply imputation rules.

8.2.2. Missing data handling for safety data

For categorical variables, subjects with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of subjects with missing data is presented.

8.2.2.1. Missing/Partial dates in adverse events and concomitant medications/therapies

8.2.2.1.1. Missing start date

Missing day only

- If the month and year are the same as the month and year of the first dose date, the day of first dose date will be used.
- If the month/year is before the month/year of the first dose date, the last day of the month will be used.
- If the month/year are after the month/year of the first dose date, the 01 will be used.

Missing day and month

- If the year is the same as the year of the first dose date, the first dose date will be used.
- If the year is prior to the year of the first dose date, December 31 will be used.
- If the year is after the year of the first dose date, January 1st will be used.

Missing day, month, and year

- No imputation can be done.

After missing date were imputed for an AE, if the AE is not the first record in a series of events for the same AE, and the imputed date is earlier than the start date of the previous record, then use the start date of the previous record instead.

8.2.2.1.2. Missing end date

Missing day only

- The last day of the month will be assigned as the missing day.

Missing day and month

- December 31 will be assigned to the missing fields.

Missing day, month, and year

- The event will be regarded as ongoing and the date cannot be imputed.

Unless the status of the end is ongoing, all the imputed dates will be compared against the End of Study date, death date, and data cut-off date. The earliest one will be used.

8.2.2.2. Missing/Partial Dates at Screening Visits

The following rules apply to dates recorded during the screening visits (e.g., prior anticancer therapy).

Missing day only

- The first day of the month will be used.

Missing day and month

- If the year is the same as the year of the earliest inform consent date at screening, the 1st of January will be used.
- If the year is before the year of the earliest inform consent date at screening, the 15th of June will be used.

Missing day, month and year

- No imputation can be done.

If the imputed end date is before the start date, the start date will be used as the end date. If the imputed dates are after the inform consent date at screening, then the inform consent date will be chosen.

8.2.2.3. Missing/Partial Dates in Exposure

No imputation will be done for the date of the first dose of study drug.

If the date of the last dose of study drug is missing or partially missing, it will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment Disposition eCRF page for the study drug AND there is no death date, the subject should be considered to be ongoing and the data cutoff date for the analysis will be used as the last dosing date.
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page for the study drug OR a death date (on or before the data cutoff date), then the imputed last dose date is:
  - Last day of the year, if only the year is available and Year<Year of min(EOT date, death date).
  - Last day of the month, if both the year and month are available and Year=Year of min(EOT date, death date) and Month <Month of min(EOT date, death date).
  - min(EOT date, death date), for all other cases.

8.3. Appendix C: EORTC QLQ-C30 and QLQ-BIL21 scales and scores

Table (8.3) 1 – EORTC QLQ-C30

	Number of Items	Item Range	Version 3.0 Item Numbers
Global health status	2	6	29, 30
Functional scales			
Physical functioning	5	3	1 to 5
Role functioning	2	3	6, 7
Emotional functioning	4	3	21 to 24
Cognitive functioning	2	3	20, 25
Social functioning	2	3	26, 27
Symptom scales			
Fatigue	3	3	10, 12, 18
Nausea and vomiting	2	3	14, 15
Pain	2	3	9, 19
Dyspnoea	1	3	8
Insomnia	1	3	11
Appetite loss	1	3	13
Constipation	1	3	16
Diarrhoea	1	3	17
Financial difficulties	1	3	28

Note: Item range is the difference between the possible maximum and minimum response to individual items; most items take values from 1 to 4, giving range = 3.

Table (8.3) 2 – EORTC QLQ-BIL21

	Number of Items	Item Range	Item Numbers
Eating symptoms	4	3	31 to 34
Jaundice symptoms	3	3	35 to 37
Tiredness	3	3	38 to 40
Pain symptoms	4	3	41 to 44
Anxiety symptoms	4	3	45 to 48
Treatment side-effects	1	3	49
Difficulties with drainage bag/tubes	1	3	50
Concerns regarding weight loss	1	3	51

Note: Item range is the difference between the possible maximum and minimum response to individual items; most items take values from 1 to 4, giving range = 3.

For all scales, the RS (Raw Score) is the mean of the component items:

$$RS = \frac{\sum_{i=1}^{n} I_i}{n}$$

Then for Functional scales:

$$Score = \left(1 - \frac{(RS - 1)}{range}\right) \times 100$$

Where range is the possible maximum and minimum response to each item. E.g. an item scales from 1 to 4, thus range = 3.

And for other scales:

$$Score = \frac{RS - 1}{range} \times 100$$