Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study official 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
Study brief title	Not applicable
Study public title	Not applicable
Test drug code	S95031 (formerly identified as AG-120)
Indication(s)	Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation
Development phase	Phase II
Protocol code	CL2-95031-008
EU trial Number	Not applicable
Universal Trial Number	Not applicable
Other register number (ISRCTN, CT. gov…)	NCT06081829
Investigational New Drug Application Number	Not applicable
Sponsor	Institut de Recherches Internationales Servier (I.R.I.S.)
International Coordinator	Not applicable
Date of the document	13 May 2024
Version of the document	Final version
Version Number	2.0

CONFIDENTIAL

VERSION LIST

Protocol No	Substantial amendment No	Final version date	Countries concerned	Nature of modifications
1.0	NA	20 March 2023	NA	Not Applicable
2.0	1.0	13 May 2024	NA	• Incorporated modifications made in the nonsubstantial protocol amendments versions 1, 2 and 3. • Updated risk language to align with IB v14.0: Guillain-Barré Syndrome (GBS), Leukoencephalopathy including Progressive Multifocal Leukoencephalopathy (PML), Lumbosacral Plexopathy, and Posterior Reversible Encephalopathy Syndrome (PRES) were removed. • Removed text regarding PML or GBS as criteria for premature discontinuation of IMP in Section 5.5.1. • Footnote was added to Table (8.11.1) 1 for clarification.

SYNOPSIS

Name of the Sponsor: Institut de Recherches Internationales Servier (I.R.I.S.)	
Name of Finished Product: TBD (USA: 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	
Investigators: listed in a separate document	
Study centre(s): Approximately 10 study centres in Japan will participate in this study	
Study period: - Study initiation date: Sep 2023 (FVFP) - Study completion date: Estimated May 2027	**Study development phase:** Phase II

Objective(s) and endpoint(s):

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, 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), version 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 Response Evaluation Criteria in Solid Tumors (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). • 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.

Methodology:
This is an open-label, multicenter study of orally administered ivosidenib.

Subjects are required to have a histologically confirmed diagnosis of IDH1 gene-mutated cholangiocarcinoma that is not eligible for curative resection, transplantation, or ablative therapies. Subjects must have progression of disease and have received at least 1 but not more than 2 prior treatment regimens for advanced disease (nonresectable or metastatic). All subjects must have received either a gemcitabine or a 5-fluorouracil (5-FU) based chemotherapy regimen.

Each subject's course of treatment will be comprised of the following periods:

Pre-Screening Period: A banked tumor sample (the most recent one available, preferably collected within the last 3 years) or fresh tumor biopsy is required for confirmation of IDH1 gene mutation status by central laboratory testing as part of the subject's eligibility for enrolment (R132C/L/G/H/S mutation variants tested).

Pre-Treatment/Screening Period: Subjects will undergo Screening procedures to determine eligibility within 28 days prior to the start of study treatment on Cycle 1, Day 1 (C1D1), with the exception of baseline radiographic scans, which should be performed within 21 days prior to C1D1. Additional Screening procedures include medical, surgical, and medication history, radiographic evaluation to determine extent of disease (computed tomography [CT] or magnetic resonance imaging [MRI]), complete physical examination (including height/weight), vital signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS), 12-lead electrocardiogram (ECG), echocardiography (ECHO) (or by other methods according to institutional practice) for left ventricular ejection fraction (LVEF) (according to institutional standard of care), and DME related gene polymorphism analysis, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, and serum pregnancy test).

Treatment Period and End of Treatment Visit:
Subjects who meet all study eligibility criteria will receive ivosidenib orally at a dose of 500 mg once daily (QD).

Daily study treatment will begin on C1D1. Cycles are 28 days (±2 days) in duration and dosing is continuous. All subjects will continue to receive best supportive care according to institutional practice throughout the study. Study visits will be conducted every week during Cycle 1 (Days 1, 8, 15, and 22), and every other week during Cycles 2 and 3, and Day 1 of each cycle thereafter.

An End of Treatment (EOT) Visit will be 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).

Radiographic assessment (CT or MRI) for evaluation of disease response will be 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 is suspected. For subjects who discontinue study drug for reasons other than disease progression, other than withdrawal of consent, or start of another anticancer agent, an assessment will be conducted at the EOT Visit.

Target and non-target lesion selection and objective tumor response assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be performed by the Investigator(s). An independent central review of response will be conducted by an Independent Radiology Center (IRC) per RECIST v1.1. All scans will be sent to the IRC as detailed in the site-specific Imaging Core Manual (see Section 7.2.1.). HRQOL assessments will be conducted pre-dose on C1D1 and on Day 1 of every cycle thereafter until the end of treatment. After EOT visit, the HRQOL will be conducted every 12 weeks until the start of new anticancer therapy.
One additional HRQOL assessment will also be conducted at the safety follow-up visit. Health economic outcomes assessments will occur pre-dose on C1D1 Cycle 3, Day 1 (C3D1), and at the EOT Visit. Compliance assessments will occur at Cycle 2, Day 1 (C2D1), Day 1 of every cycle thereafter, and at the EOT Visit.

Subjects will be assessed at every visit for adverse events (AEs) and concomitant medications, starting from the first dose of study treatment. Toxicity severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Additional safety assessments conducted periodically throughout the study will include vital signs, physical examinations, ECOG PS, ECHO (or other methods according to institutional practice) for determination of LVEF (only if clinically indicated), ECGs, and clinical laboratory assessments (hematology, serum chemistry, and urine pregnancy test).

Blood samples for PK/PD assessments will be drawn over a 6-hour period on C1D1 and C2D1.

Additional blood samples for PK/PD assessments will be drawn at 2 hours (±10 minutes) post-dose on C1D15, pre-dose (within 30 minutes) on C3D1 and Day 1 of every cycle thereafter, and at any time during the EOT Visit.

Subjects may continue with their stud treatment until disease progression, development of other unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, until the subject is lost to follow-up, or the Sponsor ends the study, whichever occurs first.

Upon radiographic disease progression, Principal Investigators (PIs), with consult from the Sponsor, may keep the subjects on ivosidenib after the disease progression provided the subject is clinically benefitting and there is no contraindication to continuing treatment beyond progression (see Section 8.10.1.2).

Post-Treatment Follow-up Visit: A Post-Treatment Follow-Up Visit for safety will occur 28 days (no more than 33 days) after the last dose of study drug. Every effort must be made to perform protocol-specified evaluations unless consent to participate in the study is withdrawn. If a subject's dose is interrupted for 28 days and then the subject discontinues study participation, the EOT Visit will serve as the Post-Treatment Follow-up Visit.

PFS and Survival Follow-up: Subjects who discontinue study 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. If a subject begins a new anticancer therapy during PFS follow-up, information on the new anticancer therapy will be collected.

OS follow-up assessments will occur approximately every 12 weeks after EOT unless the subject is in PFS follow-up at that time. If a subject 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. OS follow-up will continue until all subjects have died, withdrawn consent, or are lost to follow-up, or up to 24 months after the last subject enrolled, whichever occurs first.

Number of randomised/enrolled participants:
Approximately 10 Japanese subjects will be enrolled.

Diagnosis and main criteria for inclusion:
Inclusion criteria
Subjects must meet all of the following criteria to be enrolled in the study:

1. Male or female participant age ≥ 18 years old.
2. Have a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) consistent with nonresectable or metastatic cholangiocarcinoma and are not eligible for curative resection, transplantation, or ablative therapies.
3. Have 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. Have an ECOG PS score of 0 or 1.
5. Have an expected survival of ≥3 months.

6. Have at least one evaluable and measurable lesion as defined by RECIST v1.1. Subjects who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable disease falls outside of the treatment field or within the field and has shown ≥20% growth in size in the post-treatment assessment.
7. Have 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. Subjects must have received at least 1 gemcitabine- or 5-FU -containing regimen for advanced cholangiocarcinoma. Systemic adjuvant chemotherapy will be considered a line of treatment if there is documented disease progression during or within 6 months of completing the therapy.
8. Have recovered from toxicities associated with prior anticancer therapy to baseline unless stabilized under medical management.
9. Have adequate bone marrow function as evidenced by:
   a. Absolute neutrophil count ≥ 1,500/mm^3 or 1.5 ×10^9/L
   b. Haemoglobin ≥ 8 g/dL
   c. Platelets ≥ 100,000/mm^3 or 100 × 10^9/L
10. Have 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. Have 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 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 may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's IRB. (Subjects who cannot respond to the EORTC-QLQ-C30, EORTC-QLQ-BIL21, or EQ-5D-5L, are provided in at this time will be permitted to enrol and not complete these HRQOL/health economic outcome instruments, assuming all other eligibility criteria are met)
13. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test before the start of therapy. Women of childbearing potential are defined as having had onset of their first menstrual period and have not undergone a hysterectomy or bilateral oophorectomy or are not naturally postmenopausal (i.e., have not menstruated at all in the preceding 24 consecutive months without any other medical reasons).
    a. In case subject is a WOCBP: woman must have been tested negative in a serum pregnancy test before the start of therapy and must 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 must also use a barrier method.

    b. In case subject is a man: man must be either vasectomized or use effective contraception. In this last case, the partner of childbearing potential must 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

Subjects who meet any of the following criteria will not be enrolled in the study:

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 occur before a period ≥ 5 half-lives of the investigational agent has elapsed.
16. Received radiotherapy to metastatic sites of disease < 2 weeks prior to C1D1.
17. Underwent hepatic radiation, chemoembolization, and radiofrequency ablation < 4 weeks prior to C1D1.

18. Have known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and have radiographically stable disease for at least 3 months prior to study entry. Note: up to 10 mg per day of prednisone equivalent will be allowed.
19. Have 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, will not affect subject outcome in the setting of current cholangiocarcinoma diagnosis.
20. Underwent major surgery within 4 weeks of C1D1 or have not recovered from post-surgery toxicities.
21. Pregnancy, possibility of becoming pregnant during the study and breast-feeding women or woman who plans to restart breast-feeding after the IMP administration/intake. Note: In the case where the Investigator has assessed that the subject may be pregnant as a result of medical interview, etc, the subject will be excluded.
22. Are taking known strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window (Appendix 6), unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing.
23. Have an active infection requiring systemic anti-infective therapy or with an unexplained fever > 38.5°C within 7 days of C1D1 (at the discretion of the Investigator, subjects with tumor fever may be enrolled).
24. Have any known hypersensitivity to any of the components of ivosidenib.
25. Have 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 (Appendix 11); myocardial infarction; unstable angina; and/or stroke.
26. Have 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. Have a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) (Appendix 8)) ≥450 msec or other factors that increase 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 are permitted with approval of the Sponsor.
28. Are taking medications that are known to prolong the QT interval (Appendix 9) unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing or unless the medications can be properly monitored during the study. (If equivalent medication is not available, QTcF should be closely monitored.)
29. Have known active hepatitis B (HBV) or hepatitis C (HCV) infections, known positive human immunodeficiency virus (HIV) antibody results, or acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed per institutional practice will be permitted.
30. Have any other acute or chronic medical or psychiatric condition, including recent (within 12 months of Day 1) or active suicidal ideation or behaviour, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.
31. Have known active inflammatory gastrointestinal disease, chronic diarrhoea, 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 is allowed (assuming no drug interaction potential).
32. Have known medical history of progressive multifocal leukoencephalopathy (PML).

Test drug:
Ivosidenib will be provided as 250 mg strength tablets to be administered orally.

Subjects will receive 500 mg QD on Days 1 to 28 in 28-day cycles. Starting with C1D1, dosing is continuous; there are no planned inter-cycle rest periods.

Comparator:
Not applicable

Duration of treatment:
Subjects may continue with their study treatment until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, lost to follow-up, or the Sponsor ends the study, whichever occurs first.

Upon radiographic disease progression, PIs, with consult from the Sponsor, may keep the subjects on ivosidenib after the disease progression provided the subject is clinically benefitting and there is no contraindication to continuing treatment beyond progression.

End of study is defined as the time until all subjects have died, withdrawn consent, been lost to follow-up, up to 24 months after the last subject enrolled, or the Sponsor has terminated the study, whichever occurs first.

Statistical Methods

The 6-month PFS rate defined as the probability of subjects who are alive and progression-free (as assessed by the IRC per RECIST v1.1) at 6 months after Day 1 (C1D1) will be used to assess the primary endpoint. Assuming a target 6-month PFS rate of 32% and a dropout rate of 10%, the study needs to enroll 10 subjects to provide approximate 84% power to reject the null hypothesis of PFS rate ≤ 2.6% using exact binomial test at 1-sided significance level of 0.05.

Efficacy analyses

The 6-month PFS rate will be estimated based on Kaplan-Meier method. An exact binomial test at 1-sided alpha of 0.05 significance level will be used for hypothesis test.

The following efficacy endpoints will be summarized by using descriptive statistics and there will be no formal statistical testing.

- ✓ Progression-free survival is 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. The primary analysis of PFS will be based on IRC response assessments. PFS based on response assessment determined by the Investigator will also be analyzed. Kaplan-Meier estimates of PFS 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).
- ✓ 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. Kaplan-Meier analysis of OS will be presented.
- ✓ OR, DOR, and TTR are also secondary endpoints and will be analyzed by the IRC for primary analysis and by the Investigator for additional analysis.

Safety analysis

Safety will be evaluated by the incidence of AEs, causality, severity, seriousness, and type of AEs, and by evaluation of vital signs, ECOG PS, clinical laboratory test results, ECGs, and LVEF data (as clinically indicated). Safety data will be provided in by-subject listings.

Pharmacokinetic pharmacodynamic analysis

Pharmacokinetic parameters will be estimated using noncompartmental analysis methods. Descriptive statistics (ie, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum, and maximum) will be used to summarize PK parameters for ivosidenib. Such parameters may include (but are not limited to) area under the concentration-time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}) and trough concentration (Ctrough). The relationships between dose and both C_{max} and AUC will be explored graphically for dose proportionality where appropriate. Descriptive statistics (ie, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum, and maximum) will be summarized for the PK concentration data over planned time points. The potential relationship between plasma levels of ivosidenib and plasma 2-HG levels will be explored with descriptive and graphical methods.

Data Monitoring Committee:

Not applicable.

Contractual signatories	
I, the undersigned, have read the foregoing protocol and agree to conduct the study in compliance with it, Good Clinical Practice and the applicable regulatory requirements. **INVESTIGATOR:**	
NAME	
CENTER NUMBER	
DATE	
SIGNATURE	
DIRECTOR OF ONCOLOGY & IMMUNO-ONCOLOGY TA:) THERAPEUTIC AREA:	
NAME	[redacted]
DATE	13 May 2024
SIGNATURE	[redacted]

Other Sponsor's signatories	
BIOSTATISTICS HEAD ONCOLOGY OR DESIGNEE:	
NAME	[redacted]
DATE	14 May 2024
SIGNATURE	[redacted]

Table of contents

List of tables

List of figures

List of appendices

List of abbreviations

Abbreviation	Definition
2-HG	2-hydroxyglutarate
5-FU	5-flurouracil
α-KG	Alpha-ketoglutarate
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0\text{-}12hr}$	Area under the concentration × time curve from 0 to 12 hours
BCRP	Breast cancer resistance protein
BID	Twice daily
BUN	Blood urea nitrogen
CCA	cholangiocarcinoma
CxDx	Cycle x, Day x
CI	Confidence interval
CIMP	Cytosine-guanine dinucleotide island methylator phenotype
C_{max}	Maximum concentration
CpG	Cytosine-guanine dinucleotide
CO_2	Carbon dioxide
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450
DDI	Drug-drug interaction
DME	Drug-metabolizing enzyme
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC-QLQ-BIL21	*European Organisation for Research and Treatment of Cancer* - Quality Of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer Module
EORTC-QLQ-C30	*European Organisation for Research and Treatment of Cancer* - Quality Of Life Questionnaire – Core Questionnaire
EOT	End of treatment
EQ-5D-5L	5-level EuroQol five dimensions questionnaire
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV, HCV	Hepatitis (B/C) virus

hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQOL	Health-related quality of life
ICH	International Council for Harmonisation
IDH, IDH1, IDH2	Isocitrate dehydrogenase protein, 1, 2
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent Radiology Center
ITT	Intent-to-Treat
IWRS	Interactive web response system
LVEF	Left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mSv	Millisievert
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OR	Objective Response
OS	Overall survival
PAS	Pharmacokinetic analysis set
PD	Pharmacodynamic
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Principal Investigator Designated Co-Investigator can act tasks on behalf of Principal Investigator to the extent permitted by GCP.
PK	Pharmacokinetic
PPS	Per protocol set
PR	Partial response
PS	Performance status
QALYs	quality-adjusted life years
QD	Once daily
QTcB, QTcF	Heart-rate corrected QT interval (using Bazett's / Fridericia's formula)
R/R	relapse or refractory
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFT	rank-preserving structural failure time
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SD	Stable disease
Signed	Signed or print name and sealed
$t_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TTR	Time to response
ULN	Upper limit of normal
WOCBP	women of child bearing potential

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non-Sponsor parties, Sponsor parties and contract research organizations responsible for local management of the study are described in a separate document entitled: “Administrative part of clinical study protocol.”

The list of Investigators is given in a separate document.

Designated Co-Investigator can act tasks on behalf of Principal Investigator to the extent permitted by GCP.

2. BACKGROUND INFORMATION

2.1. Cellular Metabolism and Cancer

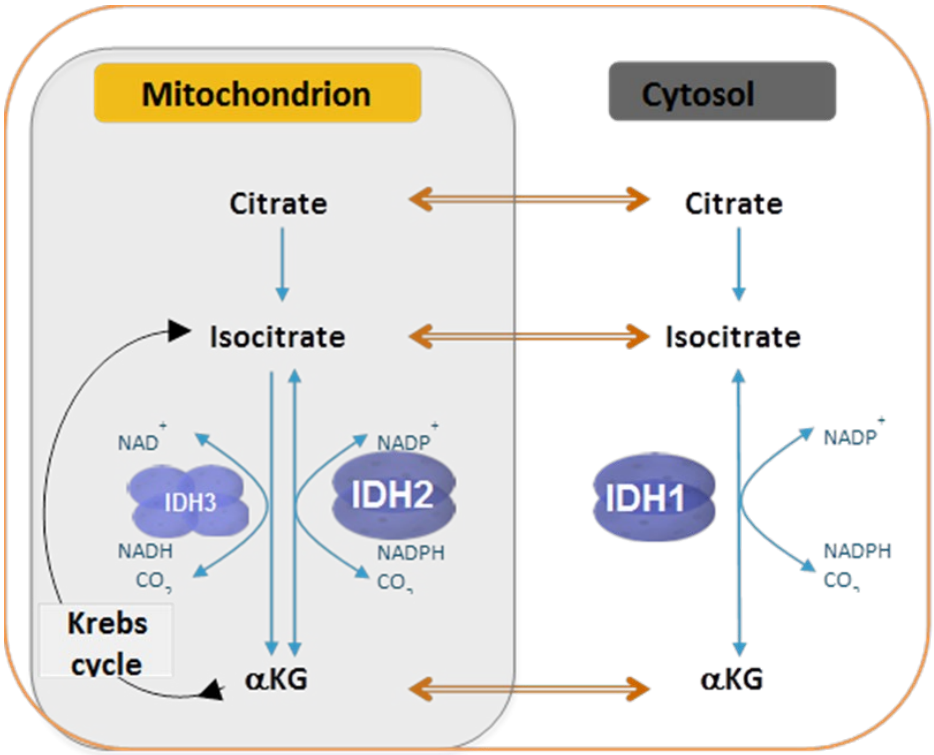
2.1.1. The Role of Isocitrate Dehydrogenase

The isocitrate dehydrogenase (IDH) proteins are critical metabolic enzymes that exist as 3 isoforms: IDH1, IDH2, and IDH3 (Figure (2.1.1) 1). All 3 catalyze the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO_2) and alpha-ketoglutarate (α-KG). IDH1 and IDH2 produce adenine dinucleotide phosphate (NADPH) whereas IDH3 only produces NADH.

Cancer-associated mutations have been identified in IDH1 and IDH2; however to date, no mutations have been described in IDH3 (Yen *et al*, 2010). One fundamental difference between IDH1 and IDH2 is the subcellular localization of the 2 proteins. IDH1 is localized in both peroxisomes and cytosol.(Geisbrecht and Gould, 1999; Yoshihara *et al*, 2001) IDH2 is a mitochondrial isoform of IDH.(Wang *et al*, 2013; Yoshihara *et al*, 2001).

The genes encoding IDH1 and IDH2 are located on chromosome 2q33.3 and 15q26.1, respectively. Mutations in these IDH proteins most commonly lead to alterations affecting arginine-132 (R132H or R132C) in IDH1, and the analogous arginine residue (arginine-172 mutated to lysine [R172K]) or arginine-140 (R140Q) in IDH2.

Figure (2.1.1) 1 - The Citric Acid Cycle



Abbreviations: CO_2 = carbon dioxide; IDH = isocitrate dehydrogenase; NADH = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate; αKG = alpha-ketoglutarate.

2.1.2. Tumorigenesis Hypothesis

Mutant IDH1 and IDH2 are not catalytically inactive enzymes, but rather possess novel enzymatic activities, consistent with a gain-of-function, reconciling the heterozygous nature of the point mutations (Dang *et al*, 2009). The mutated proteins themselves have a gain of- function, neomorphic- activity, catalyzing the reduction of α-KG to 2hydroxyglutarate (2-HG) (Dang *et al*, 2009). The Sponsor's studies established that purified mutant protein efficiently catalyzes the proposed reduction of α-KG to 2-HG, while being unable to synthesize isocitrate (Dang *et al*, 2009). Mutations in IDH1 and IDH2 are almost always mutually exclusive and occur at very early stages of tumor development suggesting that they promote formation and progression of tumors (Welch *et al*, 2012).

Evidence supports that cancer-associated IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal production of 2-HG, a potential oncometabolite. High levels of 2-HG have been shown to inhibit α–KG-dependent dioxygenases including histone and deoxyribonucleotide demethylases, which play a key role in regulating the epigenetic state of cells.(Chowdhury *et al*, 2011; Koivunen *et al*, 2012; Xu *et al*, 2011). Consistent with 2-HG promoting tumorigenesis via an effect on chromatin structure, subjects with IDH mutations display a cytosine-guanine dinucleotide (CpG) island methylator phenotype (CIMP) and several studies have shown that overexpression of IDH mutant enzymes can induce histone and deoxyribonucleic acid (DNA) hypermethylation as well as impair normal cellular differentiation (Lu *et al*, 2012; Turcan *et al*, 2012) (Figueroa *et al*, 2010).

Clinical studies in several tumor types including glioma and acute myelogenous leukemia (AML) have found elevated levels of 2-HG in cells with mutant IDH1 and IDH2 as compared to cells with wild-type alleles (Gross *et al*, 2010; Ward *et al*, 2010). In normal cells, 2-HG is present in low levels. However, IDH1/IDH2 mutations in cancer cells result in the excess accumulation of 2-HG to extremely high levels, which can alter a number of downstream cellular activities. The elevated levels of 2-HG also are present in the sera and urine of some affected subjects.

2.2. Overview of Cholangiocarcinoma

Cholangiocarcinomas (CCAs) are rare cancers (accounting for 3% of all gastrointestinal malignancies) that arise from biliary epithelium and are typically diagnosed at advanced stages for which curative surgery is not feasible. The classification of CCAs is divided anatomically as extrahepatic, intrahepatic (iCCA), and perihilar (Saha *et al*, 2014; Van Dyke et al, 2019). The disease is often advanced and incurable at the time of diagnosis. Common presentation includes symptoms related to biliary tract obstruction including jaundice, abdominal pain, weight loss, fever, fatigue, and abnormal liver function tests. The prognosis for subjects with CCA is poor; regardless of stage at diagnosis, the 5-year survival rates associated with both intrahepatic (iCCA) and extrahepatic CCA are 9% to 10% and only 2% in subjects with distant metastases (ACS, 2021). CCA (intrahepatic and extrahepatic) affects approximately 8,000 people in the US annually (ACS, 2019) and approximately 1.3 in 10,000 people in the EU (Agency, 2018). According to the 21st National Primary Liver Cancer Follow-up Survey (published in 2020), in which 546 major centers in Japan participated, which provides the latest incidence information, the number of iCCA cases obtained over 2 years was 1,332 (equivalent to 666 cases/year) and accounted for 6% of the primary liver cancer cases. National cancer statistics show 38,312 cases of primary liver cancer, and if we assume that 6% of these cases are iCCA, the annual number of subjects is 2,298 (Matsuda, 2018).

The most recent Japanese prospective study showed that the IDH1 mutation positivity rate by comprehensive genetic testing was 3% (2/66) for intrahepatic biliary tract cancer (Okawa, 2021).

As early-stage disease is commonly asymptomatic, only a minority of CCA subjects are diagnosed with resectable disease, while most of the subjects present with locally nonresectable or metastatic disease (Rizzo *et al*, 2021). The first-line and only approved standard-of-care treatment for subjects with CCA, including subjects with IDH1 mutation–positive CCA, in the locally nonresectable or metastatic setting is the combination of durvalumab with gemcitabine/cisplatin. This approval was granted in 2022 in both the US and EU and was based on the Phase 3 TOPAZ-1 trial evaluating the durvalumab and gemcitabine/cisplatin combination vs gemcitabine/cisplatin. The addition of durvalumab resulted in improved OS of 12.8 months compared with gemcitabine/cisplatin OS of 11.5 months (hazard ratio [HR] 0.80, confidence interval [CI] 0.66-0.97, p = 0.021) (Oh et al, 2022).

Second-line chemotherapy regimens produce an incrementally smaller therapeutic benefit, with an average median PFS of 2 to 3 months (Brieau *et al*, 2015; Lamarca *et al*, 2021). Overall survival outcomes are also limited to approximately 6 months (Kim *et al*, 2017; Lamarca *et al,* 2021; Matsuyama *et al*, 2018; Ying and Chen, 2019) demonstrating the need for novel treatment options in subjects with CCA.

2.3. Overview of Ivosidenib

Ivosidenib (also known as S95031, AG-120, and AGI-16678) is a potent, selective, orally active small molecule inhibitor of mutated IDH1. The clinical development of ivosidenib is being conducted worldwide, focusing on advanced hematologic malignancies as a single agent and in combination with other standard chemotherapies, and on advanced solid tumor malignancies as a single agent.

Ivosidenib (marketed in the US under the trade name TIBSOVO®) is an IDH1 inhibitor indicated for subjects with a susceptible IDH1 mutation as detected by a US Food and Drug Administration (FDA)-approved test:

- In combination with azacitidine or as a monotherapy for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
- For the treatment of adult subjects with relapsed or refractory (R/R) AML.
- For the treatment of adult patients with relapsed or refractory (R/R) myelodysplastic syndromesFor the treatment of adult subjects with locally nonresectable or metastatic CCA who have been previously treated.

Two studies investigated ivosidenib as a single agent in subjects with IDH1-mutated CCA. The results from the Phase 3 ClarIDHy study (AG120-005) and the supportive Phase 1 AG120-C-002 study demonstrate clinically meaningful and durable efficacy in subjects who received at least 1 prior line of chemotherapy.

2.3.1. Summary of Nonclinical Information

Details of the nonclinical development program for ivosidenib are provided in the Investigator's Brochure. A summary of the key information is provided below.

2.3.1.1. Toxicology Summary of Ivosidenib

The toxicity profile of ivosidenib was evaluated in vitro in a Good Laboratory Practice (GLP) bacterial reverse mutation assay, a GLP human peripheral blood lymphocyte micronucleus assay, and a GLP BALB/c 3T3 mouse fibroblast phototoxicity assay. In vivo GLP toxicology studies included repeat-dose 28-day and 3-month Sprague Dawley rat and cynomolgus monkey studies, dose range–finding and definitive embryo-fetal development studies in Sprague Dawley rats and New Zealand white rabbits, and a micronucleus study in Sprague Dawley rats. Based on the results of the nonclinical toxicology program conducted to date, ivosidenib has an acceptable safety profile for continued use in humans.

2.3.1.2. Clinical Pharmacokinetics and Pharmacodynamics

A total of 12 clinical studies have contributed to the characterization of the pharmacokinetics (PK) and pharmacodynamics (PD) of ivosidenib. Five of these studies were conducted in healthy subjects (all single-dose studies), and 7 of these studies were conducted in subjects with advanced hematologic malignancies and solid tumor malignancies (single and multiple doses). Ivosidenib demonstrated good oral bioavailability, rapid absorption, and a long elimination half-life ($t_{½}$) in subjects with IDH1-mutated AML and solid tumor malignancies, supporting a once-daily (QD) dosing regimen. The mean terminal $t_{½}$ at steady state of ivosidenib in subjects with CCA is 129 hours (102%). After multiple doses of ivosidenib, steady state was reached within 14 days, with approximately 2-fold accumulation in plasma exposure. Plasma exposure of ivosidenib increased less than dose proportionally from 100 to 1,200 mg.

Results from studies in subjects with advanced hematologic malignancies (AG120-C-001, AG120-221-C-001, and AG221-AML-005) and solid tumor malignancies (AG120-C-002, AG120-881-C-001, and AG120-C-005) indicate that plasma 2-hydroxyglutarate (2-HG) levels were substantially reduced in subjects with an IDH1 mutation (achieving levels similar to those in healthy subjects) at doses ranging from 200 to 1,200 mg QD. Multiple doses of ivosidenib also decreased 2-HG levels in bone marrow (AML) and tumor biopsies (CCA and chondrosarcoma) at doses ranging from 200 to 1,200 mg QD. Maximal plasma inhibition of 2-HG occurred at 500 mg QD in most subjects, with no additional inhibition observed at higher doses.

2.3.2. Summary of Clinical Data

The ivosidenib clinical development program was initiated in March 2014. As of the data cutoff date for Edition 14 of the IB, 16 January 2024, 20 clinical studies in adults were completed or ongoing in healthy subjects and in subjects with IDH1 mutation–positive hematologic malignancies and solid tumor malignancies. Ivosidenib is being investigated as a single agent treatment in subjects with R/R AML, newly diagnosed AML, R/R myelodysplastic syndrome (MDS), and other hematologic malignances, as well as in cholangiocarcinoma, glioma, and other solid tumor malignances, and in combination with induction/consolidation chemotherapy or azacitidine in subjects with newly diagnosed AML.

Refer to the Investigator’s Brochure for further details on each of these studies.

2.3.2.1. Study AG120-C-005

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.

In Study AG120-C-005, adults with unresectable or metastatic cholangiocarcinoma who had received 1 or 2 prior therapies were randomized 2:1 to ivosidenib (N = 126) or matched placebo (N = 61). The primary endpoint of PFS (by a blinded independent radiology center) was significantly improved with ivosidenib (median: 2.7 months; 95% CI: 1.6, 4.2 months) compared with placebo (median: 1.4 months; 95% CI: 1.4, 1.6 months), with a hazard ratio (HR) of 0.37 (95% CI: 0.25, 0.54; 1-sided P < 0.0001). Progression-free survival results were consistent across all subgroups analyzed, including sex, type of cancer, and extent of disease at screening, and favored ivosidenib

The final analysis for OS, a key secondary endpoint, numerically favored ivosidenib despite a high rate of crossover from the placebo arm (approximately 70%) but was not statistically significant (HR: 0.79; 95% CI: 0.56 – 1.12; 1-sided P = 0.093). To adjust for the effect of crossover from placebo to ivosidenib, the rank-preserving structural failure time (RPSFT) model was implemented. A statistically significant improvement in OS was observed with ivosidenib compared with placebo in this prespecified analysis (HR: 0.49; 95% CI: 0.34 – 0.70; 1-sided P < 0.0001) with an adjusted median OS for placebo of 5.1 months compared to the 10.3 months observed on the ivosidenib arm.

2.3.2.2. Study AG120-C-006

A Phase 1, Single-Dose, Open-label Trial to Evaluate the Pharmacokinetics and Safety of AG-120 in Healthy Male Japanese Subjects Relative to Healthy Male Caucasian Subjects.

Study AG120-C-006 was a Phase 1, single-dose trial to evaluate the PK and safety of ivosidenib in healthy, adult male Japanese (N = 30) and Caucasian (N = 30) subjects. Ivosidenib was well tolerated by both Japanese and Caucasian subjects. The only AEs recorded were single events of Migraine headache and Upper respiratory infection, both of which resolved and were mild or moderate in severity. There were no SAEs, treatment-related AEs, AEs leading to discontinuation of treatment, clinically significant AEs, or deaths. There were no clinically significant changes in hematology values for any of the subjects, and no clinically significant abnormal findings with respect to vital signs or ECG results. Two Japanese subjects who each received a 250 mg QD dose of ivosidenib had elevated levels of creatine phosphokinase at baseline (screening) and while on Study AG120-C-006. These subjects were asymptomatic at the time when creatine phosphokinase levels were elevated. The significance of creatine phosphokinase laboratory elevations in Japanese subjects is unknown at this time.

Both Japanese and Caucasian subjects showed a similar PK profile after ivosidenib dosing. Japanese subjects had slightly lower values for AUC0-t, AUC0–∞, Cmax, and slightly higher values for terminal elimination and oral clearance (CL/F). There was no difference in Tmax between racial groups at any dose level. Ivosidenib was slowly eliminated with mean t½ values ranging from 40.9 to 46.0 hours in Japanese subjects and from 45.8 to 64.0 hours in Caucasian subjects. The average exposure of Cmax, AUC0-t, and AUC0-∞ was lower overall by 17%, 31%, and 30%, respectively, in the Japanese subjects compared with the Caucasian subjects after a single dose of ivosidenib at 250 mg, 500 mg, or 1,000 mg. The distribution of AUC and Cmax values for Japanese subjects generally fell within the range of values for that of Caucasian subjects.

2.4. Important Identified Risks of Ivosidenib

In the clinical development program, the important identified risks of Electrocardiogram QT prolonged (all indications) and Differentiation syndrome (hematologic malignancies only) have been consistently observed and continue to be monitored to ensure that their characterization does not change. The potential risk of embryo-fetal toxicity, continues to be monitored and further characterized.

Refer to the ivosidenib Investigator's Brochure for the full details regarding the risks of ivosidenib therapy.

The study will be conducted in compliance with the protocol, GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

3. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are summarised in the Table (3) 1.

Table (3) 1 - Study objectives, endpoints and other estimand attributes

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, 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), progession 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). • 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.

4. STUDY DESIGN

4.1. Investigational Plan

4.1.1. Study plan

This is an open-label, multicenter study of orally administered ivosidenib.
Subjects are required to have a histologically-confirmed diagnosis of IDH1 gene-mutated cholangiocarcinoma that is not eligible for curative resection, transplantation, or ablative therapies. Subjects must have progression of disease and have received at least 1 but not more than 2 prior treatment regimens for advanced disease (nonresectable or metastatic). All subjects must have received either a gemcitabine or a 5-fluorouracil (5-FU) based chemotherapy regimen.

Each subject's course of treatment will be comprised of the following periods:
Pre-Screening Period: A banked tumor sample (the most recent one available, preferably collected within the last 3 years) or fresh tumor biopsy is required for confirmation of IDH1 gene mutation status by central laboratory testing as part of the subject's eligibility for enrolment (R132C/L/G/H/S mutation variants tested).

Pre-Treatment/Screening Period: Subjects will undergo Screening procedures to determine eligibility within 28 days prior to the start of study treatment on Cycle 1, Day 1 (C1D1), with the exception of baseline radiographic scans, which should be performed within 21 days prior to C1D1. Additional Screening procedures include medical, surgical, and medication history, radiographic evaluation to determine extent of disease (computed tomography [CT] or magnetic resonance imaging [MRI]), complete physical examination (including height/weight), vital signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS), 12-lead electrocardiogram (ECG), echocardiography (ECHO) (or by other methods according to institutional practice) for left ventricular ejection fraction (LVEF) (according to institutional standard of care), and clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, and serum pregnancy test).

Treatment Period and End of Treatment Visit: Subjects who meet all study eligibility criteria will receive ivosidenib orally at a dose of 500 mg once daily (QD).
Daily study treatment will begin on C1D1. Cycles are 28 days (±2 days) in duration and dosing is continuous. All subjects will continue to receive best supportive care according to institutional practice throughout the study. Study visits will be conducted every week during Cycle 1 (Days 1, 8, 15, and 22), and every other week during Cycles 2 and 3, and Day 1 of each cycle thereafter.

An End of Treatment (EOT) Visit will be 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).

Radiographic assessment (CT or MRI) for evaluation of disease response will be 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 is suspected. For subjects who discontinue study drug

for reasons other than disease progression, than withdrawal of consent, or start of another anticancer agent, an assessment will be conducted at the EOT Visit.
Upon radiographic disease progression, PIs, with consult from the Sponsor, may keep the subjects on ivosidenib after the disease progression provided the subject is clinically benefitting and there is no contraindication to continuing treatment beyond progression (see Section 8.10.1.2). Target and non-target lesion selection and objective tumor response assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be performed by the Investigator (s). An independent central review of response will be conducted by an Independent Radiology Center (IRC) per RECIST v1.1. All scans will be sent to the IRC as detailed in the site-specific Imaging Core Manual (see Section 7.2.1). HRQOL assessments will be conducted pre-dose on C1D1 and on Day 1 of every cycle thereafter until EOT. After EOT visit, the HRQOL will be conducted every 12 weeks until the start of new anticancer therapy. One additional HRQOL assessment will also be conducted at the safety follow-up visit. Health economic outcomes assessments will occur pre-dose on C1D1 Cycle 3, Day 1 (C3D1), and at the EOT visit. Compliance assessments will occur at Cycle 2, Day 1 (C2D1), Day 1 of every cycle thereafter, and at the EOT Visit.

Subjects will be assessed at every visit for adverse events (AEs) and concomitant medications, starting from the first dose of study treatment. Toxicity severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0. Additional safety assessments conducted periodically throughout the study will include vital signs, physical examinations, ECOG PS, ECHO (or other methods according to institutional practice) for determination of LVEF (only if clinically indicated), ECGs, and clinical laboratory assessments (hematology, serum chemistry, and urine pregnancy test).

Blood samples for PK/PD assessments will be drawn over a 6-hour period on C1D1 and C2D1.

Additional blood samples for PK/PD assessments will be drawn at 2 hours (±10 minutes) post-dose on C1D15, pre-dose (within 30 minutes) on C3D1 and Day 1 of every cycle thereafter, and at any time during the EOT Visit.

Subjects may continue with their study treatment until disease progression, development of other unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, until the subject is lost to follow-up, or the Sponsor ends the study, whichever occurs first.

Upon radiographic disease progression, PIs, with consult from the Sponsor, may keep the subjects on ivosidenib after the disease progression provided the subject is clinically benefitting and there is no contraindication to continuing treatment beyond progression.

Post-Treatment Follow-up Visit: A Post-Treatment Follow-Up Visit for safety will occur 28 days (no more than 33 days) after the last dose of study drug. Every effort must be made to perform protocol-specified evaluations unless consent to participate in the study is withdrawn. If a subject's dose is interrupted for 28 days and then the subject discontinues study participation, the EOT Visit will serve as the Post-Treatment Follow-up Visit.

PFS and Survival Follow-up: Subjects who discontinue study 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. If a subject begins a new anticancer therapy during PFS follow-up, information on the new anticancer therapy will be collected.

OS follow-up assessments will occur approximately every 12 weeks after EOT unless the subject is in PFS follow-up at that time. If a subject 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. OS follow-up will continue until all subjects have died, withdrawn consent, or are lost to follow-up, or up to 24 months after the last subject enrolled, whichever occurs first.

End of Study: End of study is defined as the time until when all subjects have died, withdrawn consent, lost to follow-up, up to 24 months after the last subject enrolled, or the Sponsor has terminated the study, whichever comes first. Final analysis for OS will be conducted at the end of the study.

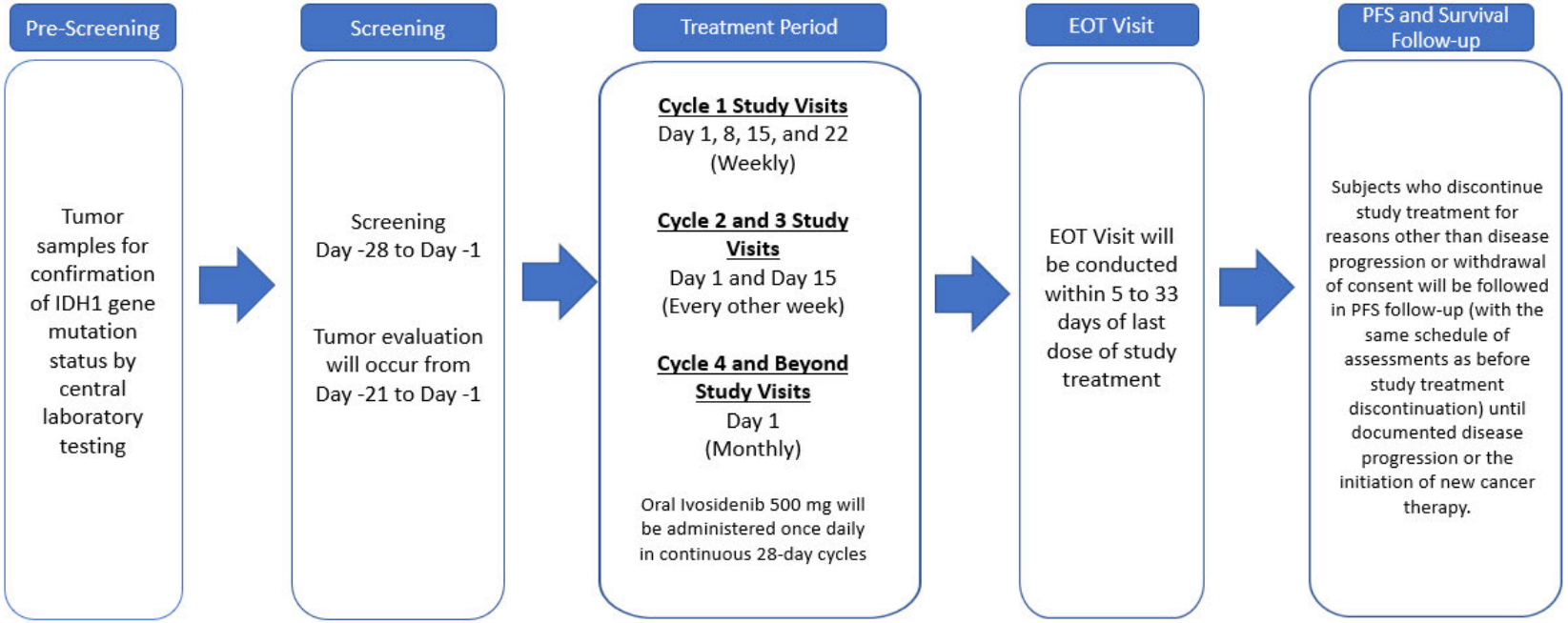
The study plan is shown in Figure (4.1.1) 1.

In case of non-inclusion of a participant, it is the Investigator's responsibility to ensure, in accordance with the local standards of care and medical practices that:

- The reason of non-inclusion is explained to the participant,
- Any event associated with any procedure/condition required by the study protocol (e.g. an event occurring following the discontinuation of a forbidden treatment) is collected,
- An adequate alternative medical care is proposed to the participant.

A non-inclusion visit is not mandatorily carried out, provided these requirements are met and documented in the medical file of the participant.

Figure (4.1.1) 1 - Study plan



If a subject 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.

.

4.1.2. Investigation schedule

Table (4.1.2) 1 describes the efficacy, safety and other assessments performed during the study.

Pre-screening or screening for IDH1m will occur at a central laboratory using either the most recent banked tumor sample (preferably from within the last 3 years) or a fresh biopsy. Subjects will undergo Screening procedures to determine eligibility within 28 days prior to the start of study treatment on C1D1, with the exception of baseline radiographic scans, which should be performed within 21 days prior to C1D1. Subjects are to attend study center visits as outlined in the Schedule of Assessments.

Study center visits will be conducted on an outpatient basis whenever possible. Subjects are to remain at the study center for 6 hours following the C1D1 and C2D1 doses for PK/PD and ECG assessments Table (4.1.2) 2. After the Screening Visit, a symptom-directed, limited physical exam should be performed at each Cycle, Day 1 visit, per institution standards of care.

An EOT Visit will be conducted as soon as possible after discontinuing study treatment (within 5 days of last dose of study treatment, if study drug dosing has not been delayed); in addition, subjects are to attend a Follow-up Visit 28 days (no more than 33 days) after the last dose of study treatment for final safety assessments. If a subject's dose is held and it is subsequently decided to discontinue treatment, the EOT Visit should be conducted as soon as possible, within 28 days (and no more than 33 days) after the last dose of study drug.

OS follow-up assessments will occur approximately every 12 weeks after EOT unless the subject is in PFS follow-up at that time. If a subject 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. OS follow-up will assess survival status and documentation of receipt and type of subsequent anticancer therapy unless consent to participate is withdrawn. If a subject begins a new anticancer therapy during PFS follow-up, information on the new therapy will need to be entered. OS follow-up will continue until all subjects have died, withdrawn consent, or are lost to follow-up, up to 24 months after the last subject enrolled, whichever occurs first. HRQOL (until the start of new anticancer therapy) assessments will be collected every 12 weeks after EOT.

Palliative radiotherapy delivered in the setting of continuation of ivosidenib beyond disease progression will require a 2-week washout period after radiotherapy before the resumption of ivosidenib treatment (see Section 6.3.5). Imaging should continue on schedule per protocol for these subjects and no additional CT or MRI will be required at the end of the 2-week washout period.

Ivosidenib should be held for the duration of palliative radiotherapy.

Hematology and serum chemistry are required at the EOT visit.

Table (4.1.2) 1 - Investigation schedule

Visit/Cycle:	Pre-Screening	Screening	Cycle 1 28 days (±2 days)		Cycle 2 28 days (±2 days)		Cycle 3 28 days (±2 days)		Cycle 4+ 28 days (±2 days)	EOT[1]	Safety Follow-up[2]	PFS Follow-up[3]	Survival Follow-up
Study Day:		D-28	D1[4]	D15	D1[4]	D15	D1	D15	D1		D+28		
Informed Consent	X	(X)[5]											
Review Entry Criteria		X											
Demographics		X											
Disease History		X											
Medical and Surgical History		X											
Medication History		X											
Complete Physical Exam		X								X			
Limited Physical Exam*			X		X		X		X				
Height[6] and Weight		X								X			
ECOG PS[7]		X	X		X		X		X	X	X		
Vital Signs[8]		X	X	X	X	X	X		X	X			
12-lead ECG	Refer to Table (4.1.2) 2 for Sampling Schedule												
ECHO (or other methods according to institutional practice) for LVEF[9]		X											
Fresh/Banked Tumor Tissue for IDH1 Mutation Status[10]	X												
Laboratory Evaluations:													
Hematology[11]		X	X	X	X	X	X	X	X	X			
Serum Chemistry[12]		X	X	X	X	X	X	X	X	X			
Coagulation Studies[13]		X											
Urinalysis[14]		X											

Visit/Cycle:	Pre-Screening	Screening	Cycle 1 28 days (±2 days)		Cycle 2 28 days (±2 days)		Cycle 3 28 days (±2 days)		Cycle 4+ 28 days (±2 days)	EOT[1]	Safety Follow-up[2]	PFS Follow-up[3]	Survival Follow-up
Study Day:		D-28	D1[4]	D15	D1[4]	D15	D1	D15	D1		D+28		
Pregnancy Test[15]		X	X		X		X		X				
Registration and Treatment:													
Study Treatment Administration[16]			X		X		X		X				
Compliance Assessment[17]					X		X		X	X			
Tumor Assessments													
Evaluate Extent of Disease and Response to Treatment[18]		X (D -21)				X			X[19]	X[20]		X	
Other Clinical Assessments													
Health-Related Quality of Life Instruments[21]			X		X		X		X	X	X	X	X
Health Economic Outcomes Assessment[22]			X				X			X			
PK/PD Assessments (Blood Sampling)	Refer to Table (4.1.2) 2 for Sampling Schedule												
Adverse Events[23]			X	X	X	X	X	X	X	X	X		
Concomitant Medications and Procedures			X	X	X	X	X	X	X	X	X		
Survival Status and New Anticancer Therapy Check[24]													X

Abbreviations: AE = adverse event; ALP = alkaline phosphatase, ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram, ECHO = echocardiography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; INR = international normalized ratio; LVEF = left ventricular ejection fraction; PD = pharmacodynamic; PFS = progression-free survival; PK = pharmacokinetic; PS = performance status; PT = prothrombin time; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumours; RTSM = Randomization and Trial Supply Management; SAE = serious adverse event; WBC = white blood cell.
Note: all cycles are 28 days (±2 days) in duration, there are no planned rest periods between cycles.

*Results from the limited physical exams will be captured in source documentation, but there is no eCRF for these exams.

1. Assessments to be conducted within 5 to 33 days of last dose of study treatment.
2. At least 28 days, and no more than 33 days after discontinuation of treatment, subjects will return to undergo review of concomitant medications, ECOG PS, and assessment for resolution of any treatment-related toxicity.
3. Subjects who discontinue study treatment for reasons other than disease progression or withdrawal of consent and are alive by EOT will enter PFS follow-up with the same schedule of assessments as before study treatment discontinuation,until documented disease progression, death, start of subsequent anticancer therapy, or withdrawal of consent.
4. Subjects are to remain at the study centre for 6 hours following the C1D1 and C2D1 doses for PK/PD and ECG assessments.
5. If, at the discretion of the site, ICFs for pre-screening and main study part are taken separately
6. Height is to be obtained only at the Screening assessment.
7. On C1D1, assessment should be conducted pre-dose.
8. Systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is seated or supine. On C1D1, assessments should be conducted pre-dose.
9. Procedure is to be conducted at Screening. The same procedure to evaluate LVEF should be conducted thereafter only if clinically indicated.
10. Subjects will have the most recent banked tumor (preferably within the last 3 years) or fresh biopsy samples available for IDH1m confirmation (R132C/L/G/H/S mutation variants tested) by central laboratory prior to receiving their first dose of study treatment. This sample can be collected at Pre-screening Visit. Around 100 microns of formalin-fixed paraffin-embedded tissue or a tumor tissue block with corresponding pathology report should be available for shipment to a laboratory designated by the Sponsor. Date of tumor tissue collection for either banked or fresh tumor samples should be recorded based on the pathology report. Detailed instructions for tumor tissue collection and shipping for central testing will be provided in a separate laboratory manual. Collect information on the records of examinations on IDH1 status, if available.
11. Hemoglobin, RBC count, WBC count, neutrophils count, lymphocytes count, and differential (% neutrophils, % bands), and platelet count. No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. On C1D1, assessments should be conducted pre-dose.
12. Sodium, potassium, total calcium, magnesium, phosphate, albumin, glucose, BUN, creatinine, uric acid, LDH, ALP, ALT, AST, total bilirubin, and direct bilirubin. No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date. On C1D1, assessments should be conducted pre-dose.
13. PT and/or INR, and activated aPTT.
14. Color, appearance, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic inspection of sediment.
15. A serum pregnancy test will be performed at Screening and a serum or urine pregnancy test will be conducted on C1D1 and confirmed negative prior dosing, and on Day 1 of all subsequent cycles. On C1D1, the test should be conducted pre-dose.
16. The drug kit number will be allocated via RTSM. The morning doses on C1D1, C1D15, C2D1, C3D1, and Day 1 of all subsequent cycles are to occur in clinic to allow for pre-dose assessments (C1D1) and to accommodate PK/PD sampling.
17. Treatment compliance is to be assessed based on return of unused drug as well as subject diaries.
18. Tumor assessments will include all known or suspected disease sites. CT imaging of the chest, abdomen, and pelvis (Torso) with contrast should be performed at baseline and on study. For subjects with allergy to IV iodine contrast, CT chest without IV contrast and MRI abdomen with IV contrast should be performed at baseline and on study. Brain scans with CT or MRI should be performed at baseline in subjects with known treated brain metastases and on study at the same imaging time points as Torso imaging. Bone scans will be performed at baseline if disease is suspected and on study at the same imaging time points as Torso imaging. Radiographic assessment (CT or MRI) for evaluation of disease response to be conducted at Screening (Day -21), every 6 weeks beginning at C1D1 (±5 days) for the first 8 assessments (ie, through week 48), and then every 8 weeks (±5 days) from C1D1, thereafter independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. All scans obtained will be sent to the IRC, as detailed in the site-specific Imaging Core Manual.

19. Extent of disease will be assessed based on RECIST v1.1.
20. If a subject goes off treatment for reasons other than disease progression, response assessments will be conducted at the EOT Visit and every 6 weeks (±5 days) for the first 8 assessments (ie, through week 48), and then every 8 weeks (±5 days) thereafter until withdrawal of consent, disease progression, death, the subject is lost to follow-up, or until the end of study/study termination.
21. EORTC-QLQ-C30 and EORTC-QLQ-BIL21, to be conducted pre-dose on C1D1. After EOT visit, the HRQOL will be conducted every 12 weeks until the start of new anticancer therapy.
22. EQ-5D-5L to be conducted pre-dose on C1D1, C3D1, and at the EOT visit.
23. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs regardless of attribution will be collected. Any SAEs that are assessed as related to study treatment that occur >28 days post-treatment also are to be reported.
24. After a subject experiences progression of disease or start of subsequent therapy, they will be contacted every 12 weeks (±7 days) thereafter for assessment of survival status (OS), HRQOL, and anticancer therapies until death, withdrawal of consent, the subject is lost to follow-up, or until the end of study/study termination, unless consent to participate is withdrawn

Table (4.1.2) 2 - Pharmacokinetic/Pharmacodynamic Sampling (2-HG) and Electrocardiogram Schedule

Visit/Cycle:	Screening	Cycle 1								Cycle 2		Cycle 3+		EOT[1]		Safety F/U
Study Day:	D-28	D1		D8		D15		D22		D1		D1		D+28		
Assessment	ECG	Blood	ECG[2]	Blood	ECG[2]	Blood	ECG[2]	Blood	ECG[2]	Blood	ECG[2]	Blood	ECG[2]	Blood	ECG[2]	ECG
Pre-dose[3]	X	X	X		X		X		X	X	X	X[4]	X			
Post-dose																
Anytime														X	X	X
0.5 hr[5]		X								X						
2 hr[5]		X	X[6]			X	X[6]			X	X[6]					
4 hr[5]		X								X						
6 hr[5]		X								X						

Abbreviations: D = day, ECG = electrocardiogram, EOT = end of treatment, F/U = follow-up.

Note: All 12-lead ECGs are to be conducted after 3 minutes of recumbency or semi-recumbency, or supine position.

1. Assessments to be conducted on the last day of study treatment (within 5 days of last dose of study drug).
2. 12-lead ECGs are to be obtained at Day 1, Day 8, D15, and Day 22 of Cycle 1 and Day 1 of each cycle thereafter. ECGs should be done before PK sampling on these days. ECGs are performed weekly for the first cycle then once monthly. ECGs are to be obtained within ±15 minutes of specified time.
3. To be obtained within 30 minutes before dose; can be done any time during Screening.
4. Blood samples to be collected at Cycle 3 and beyond, until EOT.
5. Blood samples to be obtained within ±10 minutes of specified time. Blood samples to be collected just after completion of the ECG.
6. ECG to be obtained within ±15 minutes of specified time.

For further practical details, methods of measurement are provided in Section 8.

4.2. Measures to minimise bias

The following measures will be taken in order to minimise bias:

- Analysis of samples for PK and PD will be performed in a specific central laboratory to minimise the variability of measurements.
- Screening for participants with mIDH1 will be performed based on a central evaluation with clinically validated diagnostic test.
- Evaluation of anti-tumour efficacy endpoints will be based on an IRC.
- QoL questionnaires will be completed by the subject independently of the study personnel.

4.3. Study products and Blinding Systems

4.3.1. Products administered

4.3.1.1. Description of the IMP

In this study, the IMP is ivosidenib.

The drug product is supplied as 250 mg strength film-coated (blue) tablets for oral administration. Tablets contain the inactive ingredients hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate. 250 mg film-coated tablets also include the inactive ingredient Opadry®II Blue.

Table (4.3.1.1) 1 provides a description of the IMP.

Table (4.3.1.1) 1 - Description of the IMP

	Ivosidenib
Pharmaceutical form	Tablet
Unit dosage	250 mg
Appearance, color	a blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side
Composition	Lactose monohydrate

4.3.1.2. Packaging and Labelling

Ivosidenib will be provided as 60-count bottles of 250 mg tablets. At each D1 of each cycle, subject will receive one small box containing one bottle.

4.3.1.3. Blinding Systems

This study is an open-label study. No blinding measures will be taken.

4.3.2. IMP management

IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to Section 6.2), accountability and collection are the responsibility of the Investigator and/or pharmacist of the medical institution. All these actions have to be done in RTSM as explained in the training video embedded in RSTM.

The recommended storage conditions and expiry (where required) are stated on the product label.

All investigational products must be stored in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator. IMP management will be verified on a regular basis by the study monitor.

The Investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must enter and complete in real time in RTSM and all the documents provided by the Sponsor concerning IMP management (refer to pharmacy manual).

The Investigator and/or the pharmacist of the medical institution should only use the IMP provided for the participants involved in the study.

All defects or deterioration of IMPs or their packaging are to be reported to the study monitor. The Investigator will notify the monitor of all complaints reported by a participant (change of taste, appearance, etc.).

Destruction of the IMP is the responsibility of the Sponsor and/or the Investigator and/or the pharmacist of the medical institution.

Remaining treatments (used and unused IMPs) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMP management. Used IMPs will be collected by the center at the time of preparation / administration along with the other wastes to be destroyed according to local routines.

In the event of anticipated return of IMPs to the Sponsor (batch recall), the Sponsor will prepare an information letter intended for the Investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study centre. On receipt of the letter, the Investigator and/or the pharmacist will identify the participants in possession of the IMP at the moment the incident becomes known, by using RTS or an equivalent document and will contact them immediately.

Study Treatment Storage

Ivosidenib tablets must be stored according to the package label.

All study treatment products must be stored in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator.

IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to Section 6.1.1), accountability and collection are the responsibility of the Investigator and/or pharmacist of the medical institution. All these actions have to be done in RTSM as explained in the training video embedded in RSTM or user manual or pharmacy manual.

The IMP should be stored in a secure area with restricted access. Specific storage conditions, if any, are mentioned on IMP labelling and are detailed in Investigator's brochure.

IMP management will be verified on a regular basis by the study monitor.

The Investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must enter and complete in real time in RTSM and all the documents provided by the Sponsor concerning IMP management (refer to pharmacy manual).

The Investigator and/or the pharmacist of the medical institution should only use the IMP provided for the participants involved in the study.

All defects or deterioration of IMPs or their packaging are to be reported. The Investigator will notify the monitor of all complaints reported by a participant (change of taste, appearance, etc.).

Destruction of the IMP is the responsibility of the Sponsor and/or the Investigator and/or the pharmacist of the medical institution

4.3.3. Management of blinding systems

Not applicable.

4.3.4. Method of assigning subjects to treatment

Only subjects who meet all study eligibility criteria will be received ivosidenib orally.

4.3.5. Study treatment preparation and administration

Daily treatment with ivosidenib will begin on C1D1; clinical observations will be conducted over 6 hours following the first dose of study treatment on C1D1. Dosing is continuous; there are no planned inter-cycle rest periods. Subjects should be instructed to take their QD dose at approximately the same time each day.

Subjects should be instructed to swallow tablets whole and do not chew the tablets. Subjects may take ivosidenib with or without food. Subjects should be advised that if ivosidenib tablets are taken with food, the subject should avoid grapefruit or grapefruit products and avoid consuming a high-fat meal. Please refer to examples of low-fat and high-fat meals in Appendix 11.

If the subject forgets to take the daily dose, then they should take ivosidenib within 12 hours after the missed dose. If more than 12 hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose.

Subjects will continue to receive best supportive care throughout the study.

Subjects may continue with their study treatment until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, the subject is lost to follow-up, or the Sponsor ends the study, whichever occurs first. Upon radiographic disease progression, PIs, with consult from the Sponsor, may keep the subjects on ivosidenib after the disease progression provided the subject is clinically benefitting and there is no contraindication to continuing treatment beyond progression.

4.4. Discontinuation of the study or temporary halt

4.4.1. Premature discontinuation of the study or temporary halt

After having informed the Investigator, this study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause by the Sponsor or by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or by the Competent Authorities.

Two copies of the written confirmation will be dated and signed by the Investigator. The IRB/IECs and Competent Authorities will be informed according to local regulations.

If the study is prematurely discontinued for reasons other than safety, subjects who are receiving treatment at the time the study is discontinued may remain on IMP if they are clinically benefiting. Subjects may receive nivolumab up to a maximum of 24 months. Ivosidenib may be continued for as long as the subject is receiving clinical benefit. Under some circumstances, the Investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the subject's interests.

If the study is prematurely discontinued, the on-going participants should be seen as soon as possible and the same assessments as described in Section 5.5 should be performed.

Under some circumstances, the Investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the participant's interests.

In case of study temporary halt, the study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, following approval from the IRB/IEC and/or Competent Authorities, according to local regulations.

4.4.2. Premature discontinuation of the study in an Investigator site (early site closure)

The Sponsor reserves the right to close a study site at any time for any sufficient reasonable cause at the sole discretion of the Sponsor.

The Investigator may also initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Competent Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

The IRB/IEC(s) and Competent Authorities will be informed according to local regulations.

4.4.3. Discontinuation of the study in the event of objective reached

After having informed the Investigator, the Sponsor may terminate the study before its scheduled term. The IRB/IEC(s) and Competent Authorities will be informed according to local regulations.

4.5. Source data

Source data and source documents of the study centre should be clearly identified in a specific, detailed and signed document before the beginning of the study.

5. STUDY POPULATION AND WITHDRAWAL OF PARTICIPANTS

5.1. Inclusion criteria

Participants are eligible to be enrolled in the study only if all of the following criteria apply:

Demographic characteristics

1. Male or female participant age ≥ 18 years old.

General criteria

2. Have a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) consistent with nonresectable or metastatic cholangiocarcinoma and are not eligible for curative resection, transplantation, or ablative therapies.
3. Have 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. Have an ECOG PS score of 0 or 1.
5. Have an expected survival of ≥ 3 months.
6. Have at least one evaluable and measurable lesion as defined by RECIST v1.1. Subjects who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable disease falls outside of the treatment field or within the field and has shown ≥ 20% growth in size in the post-treatment assessment.
7. Have 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. Subjects must have received at least 1 gemcitabine- or 5-FU -containing regimen for advanced cholangiocarcinoma. Systemic adjuvant chemotherapy will be considered a line of treatment if there is documented disease progression during or within 6 months of completing the therapy.
8. Have recovered from toxicities associated with prior anticancer therapy to baseline unless stabilized under medical management.
9. Have 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. Have 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. Have 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 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 may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's IRB (Subjects who cannot respond to the EORTC-QLQ-C30, EORTC-QLQ-BIL21, or EQ-5D-5L, are provided in at this time will be permitted to enrol and not complete these HRQOL/health economic outcome instruments, assuming all other eligibility criteria are met).

Sex and Contraceptive/Barrier Requirements

13. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test before the start of therapy. WOCBP are defined as having had onset of their first menstrual period and have not undergone a hysterectomy or bilateral oophorectomy or are not naturally postmenopausal (i.e., have not menstruated at all in the preceding 24 consecutive months without any other medical reasons).

    a. In case subject is a WOCBP: woman must have been tested negative in a serum pregnancy test before the start of therapy and must 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 must also use a barrier method.

    b. In case subject is a man: man must be either vasectomized or use effective contraception. In this last case, the partner of childbearing potential must 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.

Informed consent

Obtained prior any study-specific procedure as described in Section 13.3 of the protocol.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

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 occur before a period ≥ 5 half-lives of the investigational agent have 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. Have known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and have radiographically stable disease for at least 3 months prior to study entry. Note: up to 10 mg per day of prednisone equivalent will be allowed.
19. Have 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, will not affect subject outcome in the setting of current cholangiocarcinoma diagnosis.
20. Underwent major surgery within 4 weeks of C1D1 or have not recovered from post-surgery toxicities.
21. Pregnancy, possibility of becoming pregnant during the study and breast-feeding women or woman who plans to restart breast-feeding after the IMP administration/intake. Note: In the case where the Investigator has assessed that the subject may be pregnant as a result of medical interview, etc, the subject will be excluded.
22. Are taking known strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window (Appendix 6), unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing.
23. Have 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 be enrolled).
24. Have any known hypersensitivity to any of the components of ivosidenib.
25. Have 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 (Appendix 7); myocardial infarction; unstable angina; and/or stroke.
26. Have 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. Have a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) (Appendix 8) ≥ 450 msec or other factors that increase 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 are permitted with approval of the Sponsor.
28. Are taking medications that are known to prolong the QT interval (Appendix 9) unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing or unless the medications can be properly monitored during the study. (If equivalent medication is not available, QTcF should be closely monitored.)
29. Have known active hepatitis B (HBV) or hepatitis C (HCV) infections, known positive human immunodeficiency virus (HIV) antibody results, or acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed per institutional practice will be permitted.
30. Have 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 may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

31. Have 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 is allowed (assuming no drug interaction potential).
32. Have known medical history of progressive multifocal leukoencephalopathy (PML).

Prior/Concomitant therapy

For prior and forbidden concomitant medication, refer to Section 6.3

5.3. Retest management during screening period, screen failure and re-screening

A participant who has (a) laboratory result(s) that does not satisfy the entrance criteria may have the test(s) repeated providing that the Investigator judges it relevant according to the participant previous results, or medical history and if s/he considers laboratory abnormalities are likely to be transient. Results of the test(s) repeated should be obtained within the allowed screening period. In this case the participant will not be required to sign another informed consent, and the original participant ID number assigned by the Investigator will be used.

In any case, the last result available for each parameter must be considered for the participant inclusion.

Screen failure is defined as participant who does not fulfil at least one of the inclusion/exclusion criteria during the allowed screening period and consequently cannot participate in the study. In exceptional cases, individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened after agreement of the study medical monitor. If a patient is re-screened, the participant will be required to sign another informed consent, and a new participant identification (ID) number will be assigned by the investigator.

5.4. Additional information recorded at the screening /inclusion visit

Not applicable.

5.5. Participant withdrawal

5.5.1. Withdrawal criteria

Subjects have the right to withdraw from the study at any time for any reason. A subject's discontinuation of study treatment or withdrawal from the study will not jeopardize the relationship with their healthcare providers or affect their future care. This decision must be recorded in writing by the study site.

Premature discontinuation of IMP does not mean that the subject prematurely stops the participation in the study.

Subjects discontinuing study treatment for reasons other than withdrawal of consent from overall study participation will be expected to continue in the study including safety follow-up visits and be contacted for survival follow-up.

Should a subject decide to withdraw, all efforts will be made to complete and report the protocol defined study observations as completely as possible and to determine the reason for withdrawal.

In the event a subject discontinues study treatment or withdraws from the study, the Sponsor must be informed. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

When a subject discontinues study treatment or withdraws from the study, the primary reason for discontinuation or withdrawal must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report final study observations as thoroughly as possible.

Criteria for premature discontinuation of IMP are:
Subjects may discontinue or be discontinued from study treatment at any time. In this situation, a subject without documented progressive disease by the Investigator should be followed for tumor assessments until the development of progressive disease and/or survival.

The reasons for premature study treatment discontinuation are:

- Adverse events, according to the judgment of the Investigator, including no recovery in safety parameters
- Certain adverse events (as described in Section 8.11.1 including instances of Grade 4 QTcF prolongation.
- Disease progression (subjects who are, in the opinion of the Investigator, benefitting from treatment [e.g., slow progression] may be allowed to continue study treatment with approval of the Sponsor)
- Physician decision (for reasons that cannot be included in any of the criteria listed above)
- Pregnancy (for reporting see Section 8.8),
- Major protocol deviation if it interferes with the study evaluations and/or if it jeopardises participant's safety, *e.g.*, any medical event requiring administration of an unauthorized concomitant treatment
- Withdrawal of consent (only for IMP discontinuation): subjects will be asked if they are willing to continue the safety and disease/survival follow-up.

All AEs should be followed until resolution or for a period of 28 days from the last dose of study treatment, whichever is shorter. If the subject withdrew from treatment because of an AE, every effort must be made to perform protocol-specified safety follow-up procedures.

Information to be collected during the last visit of these participants is given in Section 5.5.2. These follow-up modalities are used to ensure the efficacy and safety evaluation of all participants who received the IMP.

Criteria for premature study discontinuation:

- Withdrawal of consent: Subjects may leave the study at any time for any reason if they wish to do so, without consequence. If a subject withdraws consent from overall study

participation (and not just study treatment), no further evaluations should be performed, and no attempts should be made to collect additional data.
- Death.
- Lost to follow-up.
- Study terminated by Sponsor.

5.5.2. Procedure

In the case of premature study discontinuation due to an adverse event (event requiring immediate notification or not), the Investigator must make every effort to collect the information relating to the outcome of the event. If necessary, the information will be collected afterwards (see Section 8.8.1.1). This information is recorded in that part of the electronic case report form which concerns adverse events. If the Investigator cannot collect the information from a visit, he must collect it from the doctor ensuring the follow-up of the participant.

If the study is stopped / IMP is discontinued as a result of an event requiring immediate notification, the procedure described in Section 8.8.1.5 is to be implemented.

The dispositions to be taken after the IMP discontinuation are described in Section 6.5.

5.5.3. Lost to follow-up

When the Investigator has no news of the participant, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones, etc.), to establish the reason for the discontinuation of IMP and to suggest the participant comes to a withdrawal visit. If all these attempts to contact the participant fail, the Investigator can then declare the participant “lost to follow-up”. The Investigator should document all these attempts in the corresponding medical file.

6. TREATMENT OF PARTICIPANTS

6.1. IMPs administered

Ivosidenib will be administered orally at a dose of 500 mg (provided as 250 mg strength tablets).

Each day, the subject will take 2 tablets of 250 mg ivosidenib at the same time, preferably in the morning, in fasting or non-fasting conditions.

For treatment dose adaptations due to toxicities, please refer to Section 8.10.
All the IMP tracking are managed in RTSM in real time. The procedures to be followed by the Investigator or authorised person are detailed in the training video embedded in RSTM or user manual.

6.1.1. Treatment Duration

Treatment with ivosidenib will continue until disease progression, development of other unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, the subject is lost to follow-up-, or the Sponsor ends the study, whichever occurs first. Upon radiographic disease progression, PIs, with consult from the Sponsor, may keep the subjects on ivosidenib after the

disease progression provided the subject is clinically benefitting and there is no contraindication to continuing treatment beyond progression.

Following discontinuation of study treatment, subjects are to attend a Follow-up Visit at least 28 days and no more than 33 days after the last dose for study assessments. When study treatment is withheld from a subject in order to resolve toxicity and the subject does not subsequently restart treatment, EOT is defined as the date when the study drug was first held. Subjects should proceed with EOT assessments, safety, PFS, and survival follow-up. If the decision to not restart study treatment occurs outside of the 28-day safety follow-up window, the subject should proceed with PFS and survival follow-up.

Subjects will be contacted approximately every 12 weeks after EOT to assess survival status, HRQOL (until the start of new anticancer therapy), and to document receipt of subsequent anticancer therapy unless consent to participate is withdrawn.

6.2. IMP dispensing

The Investigator may only use the IMPs provided for the participants involved in the study and treated under his/her responsibility.

IMPs will be allocated, dispensed, and tracked via RTSM by the pharmacist/responsible of the healthcare establishment upon prescription of the Investigator only. The Investigator may only use the IMPs provided for the subjects involved in the study and treated under his/her responsibility

The pharmacist/responsible of healthcare prepares the treatment and document it in the drug kit tracking file or equivalent validated tracking system. Then either sticks the drug kit label in the paper label collection form or assigns drug kit number in the validated electronic tool based on site procedures or scans QR code in the validated electronic tool at site level to log the dispensation.

All dosages of IMPs prescribed to the subject and all dose changes during the study must be done via RTSM to obtain the treatment number to be dispensed

Drug Kit will be identified by a 6-digit number for identification, tracking and stock management purposes.

6.3. Previous and concomitant treatments

6.3.1. Previous medications and procedures

All medications administered and procedures conducted within 28 days prior to the first day of study treatment administration are to be recorded on the eCRF. In addition, all prior treatments for the underlying malignancy should be recorded.

A list of prohibited and unauthorized treatments by drug class can be consulted in the eCRF.

6.3.2. Concomitant therapy requiring careful monitoring

Concomitant use of drugs with a potential QT prolongation should be avoided and replaced with alternative treatments. If this is not possible, subjects receiving these drugs should be adequately monitored.

These medications include but are not limited to:

- Fluoroquinolones such as ciprofloxacin and moxifloxacin
- Azole antifungals such as fluconazole and posaconazole
- Serotonin (5-HT_3) antagonists such as granisetron and ondansetron

Other examples of drugs known to prolong the QT interval are listed in Appendix 9.

Systemic administration of moderate or strong CYP3A4 inhibitors (Appendix 6) requires careful monitoring of the QTc.

6.3.3. Prohibited concomitant therapy

Anticancer therapy other than the treatment outlined in the protocol is not permitted during the study. If alternative therapy is required for treatment of the subject's disease, the subject should be discontinued from the study treatment.

6.3.4. Drug-drug interactions

Ivosidenib is mainly metabolized by CYP3A4 and, therefore, subjects should not use strong CYP3A4 inducers (Appendix 6) during treatment with ivosidenib.

Ivosidenib clinical trials and physiologically based pharmacokinetic (PBPK) simulations have shown that ivosidenib plasma concentrations increase with co-administration of a strong or moderate CYP3A4 inhibitor (Appendix 6), and increased ivosidenib plasma concentrations may increase the risk of QTc prolongation. Therefore, alternative therapies that are not strong or moderate CYP3A4 inhibitors should be considered during treatment with ivosidenib. If concomitant use of strong or moderate CYP3A4 inhibitors is unavoidable, subjects should be monitored for increased risk of QTc prolongation.

Ivosidenib is an inducer of human CYP3A4/5 and may also induce CYP2B6, CYP2C8, and CYP2C9. Therefore, medications of sensitive CYP3A4 substrates with a narrow therapeutic window (Appendix 6) should be avoided unless the subject can be transferred to other medications prior to enrolling. Consider alternative therapies that are not sensitive substrates of CYP2C9 (eg, phenytoin, warfarin). Monitor coagulation values more frequently in subjects receiving warfarin (a CYP2C9 substrate) during initiation or discontinuation of ivosidenib.

Ivosidenib is an inhibitor of OAT3. A PBPK simulation predicted an increase (< 30%) in the AUC of a sensitive OAT3 substrate, suggesting that the potential for clinically relevant drug interactions due to the inhibition of OAT3 appears to be low.

Coadministration of ivosidenib may decrease the concentrations of hormonal contraceptives. Consider alternative methods of contraception in subjects receiving ivosidenib.

6.3.5. Allowed concomitant medications, procedures, and treatments

Medications and treatments other than those specified above are permitted during the study. All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care.

If clinically indicated, palliative biliary decompression procedures will be permitted on-study after discussion with the Sponsor.

Subjects should receive analgesics, antiemetics, anti-infectives, antipyretics, blood products, and any other best supportive care measures (excluding anticancer therapy) as necessary, assuming no drug interaction potential.
Palliative radiotherapy for symptomatic non-target lesions that cannot otherwise be medically managed will be permitted after Sponsor approval after disease progression has been verified, and in the setting of continuation of ivosidenib beyond disease progression.

Growth factors (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]) can be used to support subjects who have developed dose-limiting Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection.

All concomitant medications and any procedures performed during the study, including those used to treat AEs, are to be reported on the eCRF.

6.4. IMP Compliance

Subjects will be dispensed the appropriate number of Sponsor-packaged, labeled bottle(s) for at least 28 days(± 2 days) of dosing on Day 1 of each cycle. The subject will be asked to return all bottles and unused tablets (or empty bottles) on Day 1 of each cycle or at their next study visit for assessment of compliance with the dosing regimen.

Subjects will be given a Sponsor- and IRB-approved dosing diary for each treatment cycle. They should record relevant information regarding their study treatment in the diary (eg, confirmation that each daily dose was taken, reasons for missed doses). Treatment compliance will be assessed based on return of unused drug and the dosing diary.

If the participant did not bring back all ivosidenib dispensed at the previous visit, the Investigator must estimate the number of IMP units taken by the participant since the previous visit, by questioning him/her.

6.5. Discontinuation of the IMP

After the discontinuation of the IMPs, participant’s treatment is left to the physician’s discretion.

Specific rules may be followed in some countries according to local regulation.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy measurements

The tumour assessments to be performed during the study are indicated Methods and measurement times in Table (4.1.2) 1.

7.2. Methods and measurement times

The efficacy of ivosidenib will be evaluated by assessing response to treatment according to RECIST v1.1 (Eisenhauer *et al*, 2009) (Appendix 3).

Radiographic assessments (CT or MRI) to obtain tumor measurements are to be conducted at Screening (Day -21), every 6 weeks (±5 days) for the first 8 assessments (i.e., through week 48), and every 8 weeks thereafter (±5 days) from C1D1, independent of dose-delays and/or dose interruptions, and/or at any time when progression of disease is suspected. CT imaging of the chest, abdomen, and pelvis (Torso) with IV contrast should be performed at baseline and on study. For subjects with allergy to IV iodine contrast, CT of the chest without IV contrast and MRI of the abdomen with IV contrast should be performed at baseline and on study. Brain scans with CT or MRI should be performed at baseline in subjects with known treated brain metastases and on study at the same imaging time points as Torso imaging. Bone scans will be performed at baseline if disease is suspected and on study as appropriate as the same imaging time points as Torso imaging. Any ancillary findings on the radiographic assessments will be communicated to the appropriate physician for notification to the subject.

The same method (CT or MRI) should be used consistently for any given subject. For subjects permitted to continue on ivosidenib beyond documented radiographic progression, a new baseline imaging assessment will not be required, and the imaging assessments will continue on the current schedule. For subjects who discontinue study drug for reasons other than disease progression, a response assessment will be conducted at the EOT Visit. Subjects who have not experience disease progression and are alive by EOT will enter PFS follow-up with the same schedule of assessments as before study treatment discontinuation, until documented disease progression, death, start of subsequent anticancer therapy, withdrawal of consent, loss to follow-up, or until the end of study/study termination.

OS follow-up assessments will occur approximately every 12 weeks after EOT unless the subject is in PFS follow-up at that time. If a subject 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. OS follow-up will assess survival status and documentation of receipt and type of subsequent anticancer therapy unless consent to participate is withdrawn. If a subject begins a new anticancer therapy during PFS follow-up, information on the new therapy will need to be entered. OS follow-up will continue until all subjects have died, withdrawn consent, or are lost to follow-up, up to 24 months after the last subject enrolled, whichever occurs first. HRQOL (until the start of new anticancer therapy) assessments will be collected every 12 weeks after EOT.

All scans should be sent to the IRC, as detailed in the site-specific Imaging Core Manual. A central review of collected images may be conducted by an independent review committee. This independent review will not be used for treatment decisions.

7.2.1. Independent radiology center

An independent radiology review will be conducted at an IRC. The IRC will be chartered to evaluate response assessment independently per RECIST v1.1.

A detailed study-specific Imaging Core Manual will be made available to sites regarding scan acquisition requirements. All radiological scans acquired at all scheduled time points and any additional (unscheduled) radiological images acquired to evaluate for potential metastatic disease also must be sent to the IRC.

7.2.2. Health-related quality of life instruments

Subjects will complete the EORTC-QLQ-C30, and EORTC-QLQ-BIL21, instruments prior to dosing on C1D1; subjects will complete the EORTC-QLQ-C30, and EORTC-QLQ-BIL21 prior to dosing on Day 1 of every cycle thereafter until EOT. After EOT visit, HRQOL should be assessed every 12 weeks until the start of new anticancer therapy. One additional HRQOL assessment will also be conducted at the safety follow-up visit.

Completion of the questionnaires takes approximately 12 to 17 minutes. During the follow-up period (PFS and/or OS), sites should follow up with subjects to encourage them to complete the HRQOL questionnaires. During this time, the HRQOL instruments will be available online as a means to minimize missing entries and lost data.

The EORTC-QLQ-C30 is a validated general questionnaire administered to assess HRQOL in subjects with cancer. The EORTC-QLQ-BIL21 was specifically designed to measure subject-reported issues related to symptoms, disease, and treatment in subjects with cholangiocarcinoma and gallbladder cancer.

7.2.3. Health Economic Outcomes Assessment

Subjects will complete the EQ-5D-5L prior to dosing on C1D1, C3D1, and at the EOT Visit. There are index-based values (“utilities”) that are a major feature of the EQ-5D-5L instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of healthcare interventions.

The EQ-5D-5L is a validated generic health status measure used in clinical trials in cancer that consists of 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale. The descriptive system comprises five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The five-level version of the descriptive system will be used in this study (no problems, slight problems, moderate problems, severe problems, or extreme problems). The EQ visual analogue scale records the subject’s self-rated health on a vertical visual analogue scale, where the endpoints are labelled “The best health you can imagine” and “The worst health you can imagine.”

8. ASSESSMENT OF SAFETY

All AEs and other situations relevant to the safety of the participants must be followed up and fully and precisely documented to ensure that the Sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

8.1. Specification of safety parameters

Safety measurements performed during the study are indicated in Table (4.1.2) 1.

8.2. Methods and measurement times

8.2.1. Vital signs

Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, will be obtained at Screening, Days 1 and 15 of Cycles 1 and 2, on Day 1 of each treatment cycle thereafter, and at the EOT Visit. Assessments should be conducted while the subject is seated or supine. On C1D1, assessments should be conducted pre-dose.

8.2.2. Physical examination and ECOG performance status

A complete physical examination, including assessment of weight and could include a neurological exam, will be obtained at Screening and at the EOT Visit. A limited physical examination should be completed on Day 1 of each treatment cycle. Height will be obtained at the Screening Visit only. Subjects should be monitored for rash at physical examinations and during assessments of adverse reactions.

Determination of ECOG PS will be performed at Screening, on Day 1 of each treatment cycle thereafter, at the EOT Visit, and at the Safety Follow-up Visit. See Appendix 5 for ECOG PS scoring. On C1D1, assessment should be conducted pre-dose.

8.2.3. Electrocardiogram and assessment of left ventricular ejection fraction

The 12-lead ECGs are to be obtained at Screening, pre-dose on Day 1 of Cycles 1 and 2, pre-dose on Days 8, 15, and 22 of Cycle 1, 2 hours post-dose on Days 1 and 15 of Cycle 1 and on Day 1 of Cycle 2, anytime on Day 1 of Cycle 3 and beyond, and at the EOT and at Safety Follow-up Visits. When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample (in as short a time as possible).

All ECGs should be obtained following 3 minutes of recumbency or semi-recumbency, or supine position.

Subjects are to have LVEF determined by ECHO (or by other methods according to institutional practice) as clinically indicated.

8.2.4. Laboratory assessments

Clinical laboratory evaluations are to be performed by the site's local laboratory. Prior to starting the study, the Investigator will provide to the Sponsor (or its designee) copies of all laboratory certifications and normal ranges for all laboratory parameters to be performed by that laboratory.

Clinical laboratory evaluations are to be conducted according to the Schedule of Assessments. Clinical laboratory evaluations may be collected up to 24 hours prior to study visit as long as the labs were collected within the visit window (±2 days). In addition, all clinically significant

laboratory abnormalities noted on testing will be followed by repeat testing and further investigated according to the judgment of the Investigator.
The safety laboratory parameters to be evaluated by the Investigator are:

Hematology:	Hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils count, lymphocytes count and differential (% neutrophils, % bands), platelet count
Chemistry:	Sodium, potassium, total calcium, magnesium, phosphate, albumin, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), AST, 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.

Blood for hematology and chemistries is to be obtained at Screening, on Days 1 and 15 of Cycles 1-3, on Day 1 of every treatment cycle thereafter, and at the EOT Visit. If assessments for hematology and serum chemistry were performed within 3 days prior to C1D1, these do not need to be repeated at the C1D1 Visit. On C1D1, assessments should be conducted pre-dose.

Blood samples for coagulation studies and urinalysis are to be obtained at Screening only.

Pregnancy Test: All women of child-bearing potential must have a negative pregnancy test to be eligible. 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 treatment administration before dosing and on Day 1 of every cycle. On C1D1, the test should be conducted pre-dose.

***Note*: more frequent pregnancy tests should be performed if required by local law or as clinically indicated.**

8.3. Definition of adverse events

An AE is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the IMP and/or experimental procedures, occurring or detected from the date the participant signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (e.g. run-in period) are also concerned).

An AE can therefore be:

- any unfavourable and unintended sign (including an abnormal finding from an additional examination such as laboratory tests, X-rays, ECG, …) which is deemed clinically relevant by the Investigator,
- any symptom or disease,
- any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity),
- fatal studied disease progression,

and detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in participant's diary or safety evaluation scale).

Of note:

- Any **hospitalisation for administration of anti-tumoral treatment and/or associated protocol (during or after the study) or other care measures for cancer (e.g. overnight hospital stay to receive a blood or platelets transfusion), for social reasons, educational purpose** (e.g. learning of diabetes management by the participant) or routine check-up should not be considered as an adverse event and should not be reported in the e-CRF.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the studied disease should not be considered as an adverse event unless judged by the Investigator to be more severe than expected for the participant's condition.
- A non-fatal studied disease progression should not be considered as an adverse event.
- The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, **should not be reported in the e-CRF and kept in the source data (or participant file):**
  - therapeutic procedures related to a non-aggravated medical history (e.g. cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study),
  - prophylactic procedures (e.g. sterilisation, wisdom teeth removal),
  - comfort procedures (e.g. cosmetic surgery),
  - control procedures of a pre-existing condition without aggravation (e.g. colonoscopy to control the remission of colon cancer).

8.3.1. Death

Deaths occurring during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of cholangiocarcinoma should be recorded only on the Treatment and Study Discontinuation eCRFs. All other on-treatment deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and reported to the Sponsor within 24 hours.

Death should be considered an outcome and not a distinct event. The underlying medical diagnosis or suspected diagnosis that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only 1 such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

All deaths, including deaths that occur after the signing of the ICF but prior to the first IMP administration, will be collected. All on-treatment deaths (within the 28 days after last dose of study treatment) should have an associated SAE captured for the event that led to death, except in the event of disease progression.

During post-treatment survival follow-up, all deaths will continue to be collected, but only those unrelated to disease progression will be classified as SAEs.

8.3.1.1. Progression of cholangiocarcinoma

Progression of cholangiocarcinoma should not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST v1.1 (Appendix 3). Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the subject's underlying cholangiocarcinoma or does not fit the expected pattern of progression for the disease. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

8.3.1.2. Preexisting medical conditions

A preexisting medical condition is one that is present at the Screening Visit for this study. Such conditions should be recorded on the Medical History eCRF. A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse

Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

8.4. Definition of serious adverse events

Any adverse event that at, any dose:
- results in death,
- is life-threatening[(1)],
- requires inpatient hospitalization or prolongation of existing hospitalization,
- is medically significant[(2)],
- results in persistent or significant disability/incapacity[(3)],
- is a congenital anomaly/birth defect[(4)].

[(1)] Life-threatening in this context refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[(2)] Any event that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The Investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to Sponsor.

[(3)] Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

[(4)] Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

8.5. Definition of overdose

This refers to any intake of a quantity of IMP or a product other than the IMP taken as part of the protocol which is above the maximum dose recommended in the study protocol, independently of the occurrence of any AE.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol.
An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects.

Any study treatment overdose or incorrect administration of study treatment should be noted on the Study Drug Administration eCRF.

8.6. Definition of adverse event of special interest

An adverse event of special interest (AEOSI) is one of scientific and medical interest or concern regarding the IMP for which recording rules, special documentation such as hospital records and/or adjudication committee could be appropriate. It may be a serious or non-serious AE that may require further investigation in order to be characterized and understood.

AEOSI include:
Any QT prolongation event assessed as Grade 2 or worse (e.g., QTcF interval longer than 480 msec or any QTcF interval variation that is equal or more than 60 msec than the reading at baseline) with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, irrespective of the seriousness of the event, should be reported as an AEOSI to the Sponsor within 24 hours. See Section 8.11.1 for further details on managing subjects with QTcF Prolongation. See Appendix 8 for Fridericia's formula.

8.7. Classification of an adverse event (seriousness, severity, causality, expectedness)

It is important that the Investigator gives his/her own opinion regarding the **seriousness**, the **intensity** of the event as well as the **cause-effect relationship** between an adverse event and the research or disease progression. This evaluation must be assessed by the Investigator and reported in the AE form. In addition, the Sponsor will be responsible for the evaluation the **expectedness** of the event (see Section 8.8.2).

The Seriousness should be evaluated according to international guidance (see definition Section 8.4). It is under Investigator's responsibility to evaluate the AE seriousness according to international guidance (see ICH Topic E2A and EU DIRECTIVE 2001/20/EC of 4 April 2001 or further regulation (EU) No 536/2014). The Sponsor will review the AE seriousness. The seriousness may be upgraded (but never downgraded).

The severity of all AEs will be graded according to the NCI-CTCAE on a five-point scale (Grade 1 to 5):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[1].
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

The cause-effect relationship

The Investigator must make an assessment in the AE form whether the AE is related or not to the research, meaning:

- a procedure scheduled in the study protocol (i.e. exercise test, MRI, etc.), or
- a change or withdrawal of previous / concomitant treatment related to the conditions of the protocol or
- a product other than the IMP, taken as part of the protocol;

Moreover, the Investigator has to assess if the AE is related to disease progression. Cases ticked "related" by the Investigator or judged by the Sponsor as having a reasonable suspected causal relationship to the IMP (AE linked to the MoA of the IMP…), will be considered as suspected Adverse Drug Reaction. In general, if a relationship between AE and IMP is at least reasonably possible (*i.e.* the relationship cannot be ruled out) it is to be considered as "related".

If in the Investigator's opinion there is a causal relationship with the IMP, the AE must be considered as related to study protocol.

8.8. Reporting procedures

8.8.1. Time frame for AE reporting

- Any event meeting the above mentioned definitions (see Sections 8.3 and 8.6) must be reported to the Sponsor on an adverse event form if it occurred from the date the participant signs the information and consent form and:After informed consent has been obtained but prior to administration of the first IMP, only SAEs caused by a protocol-mandated intervention should be reported (eg, SAEs related to invasive study procedures such as biopsies).
- At any time after the first administration of IMP up to the participant's last IMPs administration for all events regardless of attribution
- After the participant's last IMP administration:

- At least 28 days but no more than 33 days after the participant's last IMPs administration for all AEs, regardless of the supposed role of the research.
- Irrespective of the time of onset in case of serious AE related to the research.

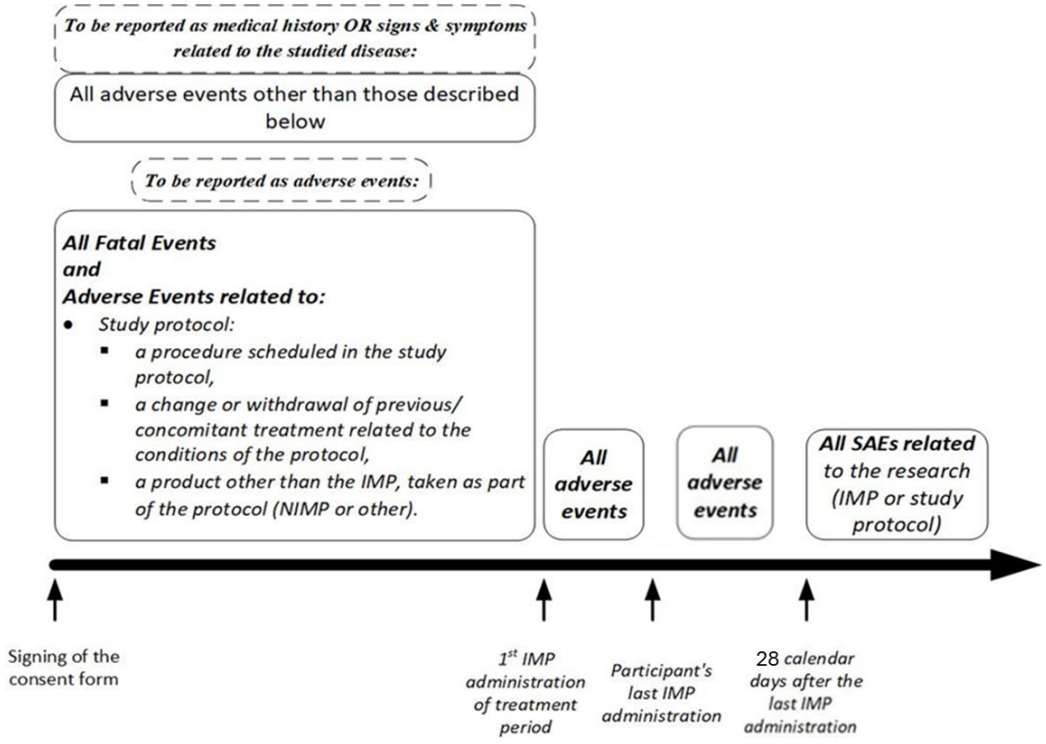
[1] Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden".

Of note, events occurring between the signature of the ICF and the first administration of the IMP for which the Investigator does not consider an association with the research must be reported **as medical history or as signs or symptoms related to the studied disease** in the dedicated form of the e-CRF.

Fatal events, related or not to the research, occurring after ICF signature and before first IMP administration, must be reported on AE form.

Figure (8.8.1) 1 - Rules for Adverse Event reporting



8.8.1.1. Documentation of the event

The Investigator must ensure that all events are well documented. He/She should provide anonymized copies of relevant source documents and additional documents, if requested by the sponsor.

8.8.1.2. Follow-up of adverse events

The Investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, severity (improvement) intensity, seriousness, measures taken, causality or outcome regarding an AE already reported must be written up in a new complete evaluation of the event documented on the "Adverse event" page previously created for the event.

In case of worsening of severity, a new complete evaluation of the event must be documented on a new "Adverse event" form.

If the AE has not resolved at the participant's final visit, the participant must be followed up suitably and any information on the outcome of the event will be noted on the "Adverse Event" form previously created for the event.

If the follow-up of the participant is not done by the Investigator him/herself (hospitalisation, followed by a specialist or the participant's general practitioner, …), the Investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the participant.

8.8.1.3. Special situations (pregnancy, overdoses, intake of IMP by a person around the participant)

Pregnancy

If a female participant in the study becomes pregnant, the Investigator must:

- stop immediately the study treatment,
- report it on the specific eCRF pregnancy form and notify the Sponsor immediately (i.e. without delay and within 24 hours of awareness at the latest),
- Pregnancy should not be reported as AE except in the following circumstances:
    - If it is associated with an AE. This consequence itself should be reported as an AE.
    - While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE. Abnormal pregnancy outcomes (*e.g.* spontaneous abortion, death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- contribute to the follow-up of this pregnancy and provide the Sponsor with information concerning this follow-up (notably using the 2nd page of the specific paper pregnancy form).
- If the partner of a participant becomes pregnant during the study, the pregnancy should not be reported in the e-CRF. The Investigator should **immediately** contact the Sponsor (contact details provided in the Investigator's study file) who will inform him/her about the procedure to be followed.

Overdose of IMP

- In case of overdose, the Investigator should report it on the IMP administration page). Overdose should not be reported as AE except in the following circumstances:
    - The overdose is associated with an AE. This consequence itself should be reported as an AE.
    - The overdose is intentional with possible suicidal/self-harming intent should be reported as an AE regardless of sequelae.
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
    - dose details (number of units, duration. etc.) and, if multiple overdoses, details regarding other medicinal products or substance,
    - context of occurrence, i.e., intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage),
    - related signs and symptoms ("No related adverse events" to be reported otherwise),

- outcome.

- Insofar as possible, a blood sample should be collected for assay of the IMP taken.

Intake of IMP or occupational exposure by a person around the participant

This event should not be reported in the e-CRF. The Investigator should immediately contact the Sponsor (contact details provided in the Investigator's study file) who will inform him/her about the procedure to be followed.

8.8.1.4. Recording Methods in the e-CRF

Adverse events must be documented on the "Adverse Event" form of the e-CRF.

In case of chronic disease:

- if the disease is known when the participant enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event,
- On the other hand, for the following diseases, any episode will be documented as an adverse event.
- if a disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the "Adverse Event" form previously created for the eventwhich will clearly describe the diagnosis.

8.8.1.5. Procedure for an event requiring an immediate notification

In case of an event requiring an immediate notification, the Investigator must:

- **Immediately** after being informed of this event, **fill in** the **participant's medical file** as well as the **"Adverse Event" form** of the e-CRF (for SAE, and events of special interest if applicable) according to the general instructions available in the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into the eCRF, an e-mail will be immediately and automatically sent to the Sponsor. However, for special situations requiring an immediate notification the completion of the "Adverse Event" form should not be performed systematically.
- If requested by the Sponsor (person designated in the contact details provided in the Investigator's study file), provide with anonymized the documents which provide additional useful information,
- Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

Moreover, on request, the Investigator should provide the Sponsor with the documents required in 8.8.1.1.

If an adverse event initially non-serious worsens and becomes a serious adverse event, this must be reported **immediately** on an "Adverse event" form of the e-CRF.

In case the e-CRF is unavailable when the Investigator was informed of an adverse event to be notified immediately he/she should:

- **Immediately** fill in a paper "Adverse event" page:
  - For serious event on a paper "Adverse event – Initial information" page,
  - For event initially non-serious on a paper "Adverse event – Initial information" page, and the worsening leading to seriousness on a paper "Adverse event – Additional information" page,

- Immediately send the page(s) by fax or a scan of them by e-mail to the person(s) designated in the contact details provided in the Investigator's study file or outside working hours, the 24-hour phone line.
  - Immediately send them by fax （contact number will be provided on a separate document
- As soon as the e-CRF becomes available, the Investigator should enter these data in the "Adverse Event" form of the e-CRF.
- A co-Investigator designated by the Investigator can cover the above mentioned role of the Investigator when the Investigator is absent. In such a case, the Investigator must confirm what have been reported by the designated co-Investigator and inform the Sponsor parties and the head of the study centre of his/her confirmation as soon as he/she has become available.

8.8.2. Responsibilities of the Sponsor

For any AE and special situation mentioned above the Investigator must:
- **Note in the participant's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person, …) and any other relevant information which he/she has learned of the event.
- **Assess** the event in terms of seriousness, severity and causality.
- **Report the event to the Sponsor** using the AE form
- **Document** the event with additional useful information.
- Ensure the **follow-up** of the event.
- **Fulfil his/her regulatory obligations** to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.
- **Ensure the oversight on data reported** and ensure the whole content's accuracy, completeness and legibility in accordance with the GCP. The Investigator or authorised member for sign-off must confirm the authenticity of the data recorded in the e-CRF by signing-off the e-CRF in a timely manner as defined in the e-CRF guide.

Moreover, the Investigator must report to the Sponsor and/or to the IRB/IEC and/or to the Competent Authorities in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the clinical investigation.

In accordance with international guidance, the assessment of the seriousness and the causality of adverse events are usually made by the Investigator but falls also under Sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The Sponsor will review the seriousness of the adverse events and the causality of (at least) the serious adverse events, whether reported by the Investigator or upgraded by the Sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of documents providing useful information such as reports of further consultations, laboratory tests reports, reports of other examination aiding diagnosis may be asked for the event assessment. If the assessments of the Investigator and the Sponsor are different, both will be reported in the clinical study report (CSR).

In addition, the Sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMP.

Independently of the regulatory obligations of the Investigator, the Sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit /risk balance of the product, required in ICH Good Clinical Practice guidelines and local regulations, to the appropriate Authorities, to all the Investigators involved and to the trial participants involved - through the Investigators - as mentioned in Section 13.4 "Modification of the information and consent form".

8.9. Responsibilities of Data Monitoring Committee

Not applicable.

8.10. Management of treatment dose adaptations due to toxicitiesStudy Treatment Dose Modification and Stopping Criteria

8.10.1.1. Dose Modifications and Delays

For any AE, including AEs not specifically mentioned in Table (8.10.1.1) 1, the Investigator may decide to delay dosing or modify the dose of ivosidenib based on clinical judgment. These decisions should be discussed with the Sponsor prior to implementation. Dose modifications of ivosidenib from 500 mg to 250 mg will be permitted on study for management of AEs (Table (8.10.1.1) 1). If more than one AE occurs that would require a dose modification, upon resolution of all AEs to baseline or Grade 1, ivosidenib should be dose reduced to 250 mg. Re-escalation may be allowed with approval from the Sponsor.

Dose delays are discouraged, except as needed for management of AEs, dose holds during palliative radiotherapy, and washout from palliative radiotherapy. Dose delays up to 28 days will be permitted at the discretion of the Investigator in consultation with the Sponsor for reasons including management of AEs and for mitigating circumstances (e.g., planned procedures). Palliative radiotherapy delivered in the setting of continuation of ivosidenib beyond disease progression will require a 2-week washout period after radiotherapy before the resumption of ivosidenib treatment (see Section 8.10.1.3). Palliative biliary decompression procedures will be permitted on study and will not require interruption of ivosidenib.

If the subject cannot resume ivosidenib within 28 days, the subject should be discontinued from study medication. Exemptions may be considered for those subjects who are determined by the Investigator to have received clinical benefit from treatment. Other reasons for treatment termination are provided in Section 6.5. If ivosidenib is discontinued, the subject will complete the EOT and Follow-up Visits, and then enter PFS follow-up (if disease has not progressed) and survival follow-up.

If a dose is delayed for the management of an AE, the subject should resume the study at the next planned visit within a dosing cycle (eg, if the subject did not start dosing at C3D1 due to management of an AE, then dosing would be resumed at C3D1 upon resolution of the AE, not C3D15).

Table (8.10.1.1) 1 - Management of Adverse Events

Adverse Events	Action
Grade 2 nausea or vomiting (related or unrelated)	• Consider holding dose of ivosidenib until resolution of AE to Grade ≤ 1 within 28 days of supportive therapy. • Manage with supportive therapy according to the institutional standard of care. • May resume ivosidenib at same dose.
Grade 3 adverse events (related, first event)	• Hold dose of ivosidenib until resolution to Grade ≤ 1 or baseline within 28 days of supportive therapy and then resume dose. • Manage with supportive therapy according to the institutional standard of care. • If the Grade 3 AE recurs (a second time), consider reducing ivosidenib to 250 mg in consultation with the Sponsor. Re-escalation may be permitted after discussion with the Sponsor. • If the Grade 3 AE recurs (a third time) despite dose reduction of ivosidenib, then consider discontinuing ivosidenib in consultation with the Sponsor. • Discontinue ivosidenib permanently
Grade 4 adverse events (related, first event)	• Hold ivosidenib. • Manage with supportive therapy according to the institutional standard of care. • If the AE resolves to Grade ≤ 1 or baseline within 28 days, then restart ivosidenib dosing at 250 mg in consultation with the Sponsor. • If the AE does not resolve to Grade ≤ 1 or baseline within 28 days, consider discontinuing study treatment in consultation with the Sponsor. • If the Grade 4 AE recurs (a second time), despite dose reduction, ivosidenib should be discontinued in consultation with the Sponsor.

*See Table (8.11.1) 1 for specific dose modifications for QTcF prolongation.

8.10.1.2. Continuation of Treatment Beyond Radiographic Progression

In the event of radiographic progression per RECIST v1.1 but in the absence of clinical deterioration, worsening ECOG performance status, or disease progression that may compromise organ function, the subject may continue to receive study treatment with ivosidenib at the discretion of the treating physician in consultation with the Sponsor. If there is clinical deterioration or continued radiographic progression documented on subsequent imaging, treatment will be discontinued, and the subject will complete the EOT and Follow-up Visits and enter survival follow-up.

8.10.1.3. Palliative Radiotherapy After Disease Progression

Palliative radiotherapy to treat symptomatic pre-existing or new non-target lesions (per RECIST v1.1) that cannot otherwise be medically managed will be permitted after disease progression has been confirmed. Ivosidenib should be held for the duration of palliative radiotherapy. A 2-week washout from completion of radiotherapy will be required prior to starting or resuming ivosidenib. For subjects permitted to continue on ivosidenib beyond documented radiographic progression, a new baseline imaging assessment will not be required, and the imaging assessments will continue on the current schedule. All decisions to pursue palliative radiotherapy will require the Sponsor approval.

8.10.1.4. Biliary Tract Obstruction During Treatment

In the event of the development of obstructive jaundice due to biliary tract obstruction, the appropriate measures will be taken to diagnose and relieve the obstruction. Study treatment interruption is not required but will be permitted at the discretion of the Investigator.

8.11. Potential Risks

8.11.1. Guidelines for Management of QT Prolongation

The discussion of the emergency management of Torsades de pointes and its hemodynamic consequences is beyond the scope of this guideline.

Events of QTcF prolongation as defined in Section 8.6 should be reported as AEs of special interest (AESIs) to the Sponsor within 24 hours, according to expedited reporting procedures.

The following are guidelines for the management of AEs of special interest based on the ivosidenib non-clinical and clinical safety findings in subjects with solid tumors to date.

Prolongation of QTcF interval has been observed in monkeys at relatively high doses of ivosidenib and has been identified as an expected risk of treatment with ivosidenib (see the Investigator's Brochure).

Subjects may be at increased risk for the development of QT prolongation when treated with ivosidenib in combination with fluoroquinolones, azole antifungal agents, or serotonin ($5\text{-}HT_3$) antagonists. Investigators need to be vigilant; refrain from administering concomitant medications associated with QT prolongation and if no other therapeutic options are available, monitor subjects receiving study treatment with the combination of these drugs, and evaluate ECG and electrolytes (including potassium, magnesium, and total calcium) particularly in subjects presenting with nausea, vomiting, or diarrhea. Systemic administration of a moderate or strong CYP3A4 inhibitor requires careful monitoring of QTcF.

Subjects who experience prolongation of the QTcF interval to > 480 msec (CTCAE Grade ≥ 2) while receiving study treatment, should be promptly evaluated for causality of the QTcF prolongation and managed according to the following guidelines and Table (8.11.1) 1:

- Levels of electrolytes (potassium, total calcium, and magnesium) should be checked, and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects.
- If no other cause is identified and the Investigator believes it is appropriate, particularly if QTcF remains elevated (after above measures have been implemented, or as determined by the Investigator), study treatment may be interrupted, and an ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed or more frequently as clinically indicated. If QTcF has recovered or improved and the Investigator believes it is safe to do so, re-challenge with study treatment should be considered if held.
- ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTcF reduction ≤ 480 msec.

Table (8.11.1) 1 - Management of QT Prolongation by CTCAE Grade

NCI CTCAE Grade	Management
Grade 2: QTc interval greater than 480 msec to 500 msec*	• Monitor and supplement electrolyte levels as clinically indicated • Review and adjust concomitant medications with known QTc interval-prolonging effects • Interrupt ivosidenib • Restart ivosidenib at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec. • Monitor ECGs should be conducted at least weekly for 2 weeks following resolution of QTc prolongation.
Grade 3: QTc interval greater than 500 msec*	• Monitor and supplement electrolyte levels as clinically indicated • Review and adjust concomitant medications with known QTc interval-prolonging effects. • Interrupt ivosidenib. • Resume ivosidenib at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. • Consider re-escalating the dose of ivosidenib to 500 mg daily if an alternative etiology for QTc prolongation can be identified.
Grade 4: QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	• Discontinue ivosidenib permanently.

*Increase of 60 msec or more from baseline, without value of QTc interval greater than 480 msec as per table above does not link to IMP dose interruption or reduction.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Assessments related to inclusion criteria.

9.1.1. Informed Consent

A complete description of the study is to be presented to each potential subject and a signed and dated informed consent is to be obtained before any study specific procedures are performed. Subjects will sign consent form(s). A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's Institutional Review Board (IRB). If patient study consent is withdrawn, no further sample analysis will be performed thereafter and the sample will be destroyed, but the information obtained prior consent withdrawal will be retained.
Site are permitted to choose if they wish to obtain informed consent in a 2-step process (pre-screening consent for IDH1 testing and afterwards if applicable for the main study) or in a 1 step process (one main ICF covering the entire study).

9.1.2. Gene Mutation Analysis and Molecular Characterization

Tissue from a pre-treatment fresh or banked tumor biopsy will be required for all screened subjects for central laboratory IDH1m confirmatory testing (R132C/L/G/H/S mutation variants tested). Corresponding pathology reports are also required. Instructions for tumor tissue collection and shipping for central testing will be detailed in a separate study manual.

Remaining tissue samples will be kept for long-term storage for up to 10 years for potential retrospective studies related to the development of a diagnostic test to select patients for treatment with ivosidenib. Then the specimens will be discarded after 10 years. Genetic analysis will be performed by using Thermo Fisher OncomineDxTT. Results other than the presence or absence of IDH1 mutations required for inclusion in this trial will not be disclosed automatically. All analysis results will be disclosed to the investigator upon request by the investigator. Test results may be disclosed to patients at the investigator's discretion.

9.2. Measurement of drug concentration

9.2.1. Sample Collection Timepoints

Serial or sparse blood samples will be drawn before and after dosing of study treatment in order to determine circulating plasma concentrations of ivosidenib. The blood samples will also be used for the determination of 2-HG concentrations.

Blood samples will be drawn on Cycle 1 Day 1 (C1D1) and Cycle 2 Day 1 (C2D1) at the following time points: predose (within 30 minutes) and 0.5, 2, 4, and 6 hours (±10 minutes) post dose for Ivosidenib PK measurements. Additional blood samples for ivosidenib PK assessments will be drawn 2 hours (±10 minutes) post-dose on C1D15 and pre-dose (within 30 minutes before dosing) on C1D1, C2D1, C3D1 and Day 1 of every subsequent cycle (CXD1) through end of treatment and anytime during the EOT Visit. Refer to Table (4.1.2) 2. for detailed sampling schedule.

When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample such that the blood sample is collected at the nominal time (±10 minutes).

9.2.2. Sampling Methods

Blood for assessment of PK parameters of ivosidenib will be collected in plasma acquisition tubes. Every effort will be made to collect PK samples at the timepoints specified. No additional samples will be collected without formal amendment to this protocol. Analysis of the plasma samples will be performed at a central specialty laboratory using validated bioanalytical methods. A separate detailed laboratory manual specifying sample collection, processing, handling, storage, and shipment will be provided to the study sites; retention time for specimens will be specified therein.

9.3. Pharmacodynamics measurements

Samples of blood for measuring the plasma concentrations of 2-HG will be obtained on Cycle 1 Day 1 (C1D1) and Cycle 2 Day 1 (C2D1) at the following time points: predose (within 30 minutes) and 0.5, 2, 4 and 6 hours (±10 minutes) post dose. Additional blood samples for 2-HG PD assessments will be drawn 2 hours (±10 minutes) post-dose on C1D15 and pre-dose

(within 30 minutes before dosing) on C1D1, C1D8, C2D1, C3D1 and Day 1 of every subsequent cycle (CXD1) through end of treatment and anytime during the EOT Visit. Refer to Table (4.1.2) 2. for detailed sampling schedule.
Detailed instructions for the collection, handling, processing, storage and shipment conditions will be outlined in the laboratory manual (or equivalent) for the study and provided to the study sites.

10. STATISTICS

A Statistical Analysis Plan (SAP), and associated templates for Tables, Listings and Graphs, will be developed. These specifications will detail the implementation of all the planned statistical analyses in accordance with the main characteristics stated in the protocol.

10.1. Statistical analysis

10.1.1. 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. Exclusion criteria will be specified in the SAP. The PPS will be used to perform sensitivity analyses for the primary endpoint.
- 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.

10.1.2. Statistical methods

10.1.2.1. General considerations

Summaries will be produced for disposition, demographic and baseline disease characteristics, safety and tolerance, pharmacokinetics, PD biomarkers, and efficacy variables, as appropriate.

Categorical data will be summarized by frequency distributions (number and percentages of subjects). Continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). 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 (eg, 3-month, 6-month, and 12-month rates) will be produced.

PK data will be provided in by-subject listings.

The study data will be analyzed and reported in the primary clinical study report (CSR) based on all subjects' data up to the time when PFS events have been determined by Investigator assessment in all subjects. Any additional data for survival follow-up and for subjects continuing to receive study treatment past the data cutoff date for the CSR until the end of study will be reported in CSR addendums or the final CSR.

10.1.2.2. Disposition and baseline characteristics

A tabulation of the disposition of subjects will be presented, including the number included, the number treated, the reasons for treatment discontinuation, and the reasons for study discontinuation. Entry criteria and protocol deviations will be listed.

Demographic and baseline disease characteristic data will be summarized. Data to be tabulated will include sex, age, and race and ethnicity, as well as disease-specific information.

10.1.2.3. Efficacy analysis

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

10.1.2.3.1. Analysis for the Primary Endpoint

The 6-month PFS rate defined as the probability of subjects who are alive and progression-free (as assessed by the IRC per RECIST v1.1) 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.

The following hypothesis test will be conducted using exact binomial test with 1-sided significance level of 0.05 for primary endpoint:

H_{01} (null hypotheses): $\Theta_1 \leq 2.6\%$ vs. H_{a1} (alternative hypotheses): $\Theta_1 > 2.6\%$

where Θ_1 is the 6-month PFS rate.

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. Detailed censoring rules will be specified in the SAP.

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

Other analyses for PFS may be conducted and will be specified in the SAP.

10.1.2.3.2. Analyses for the Secondary Efficacy Endpoints

10.1.2.3.2.1. Overall Survival

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 will also be presented.

10.1.2.3.2.2. Progression Free Survival per Investigator

The secondary endpoint of PFS is 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.

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

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

10.1.2.3.2.3. Objective Response

For the secondary efficacy endpoints of OR, DOR, and TTR, analyses will be analyzed by the IRC for primary analysis and by the Investigator for additional analysis.

Objective response is defined as confirmed CR or confirmed PR per RECIST v1.1. Objective response rate will be calculated.

A summary of best overall response will be listed.

10.1.2.3.2.4. Duration of Response

Among responders who achieve confirmed CR or PR, DOR will be calculated from the date of the first occurrence of response to the date of first documented disease progression or death. DOR will be listed.

10.1.2.3.2.5. Time to Response

Among responders, time to response will be assessed from C1D1 to the date of first occurrence of confirmed response per RECIST v1.1. TTR will be listed.

10.1.2.4. Analyses of Health-Related Quality of Life and Health Economic Outcomes

10.1.2.4.1. Health-Related Quality of Life Analyses

The EORTC-QLQ-C30, and EORTC-BIL21 questionnaires will be used to collect data on the subject's functioning, disease-related symptoms, HRQOL, and health status. If a subject is not able to respond to EORTC-QLQ-C30, and EORTC-QLQ-BIL21 the data from those instruments will be missing throughout the duration of that subject's involvement in the study. The number and percentage of subjects with the entire questionnaire missing will be summarized. Details including the missing data handling will be specified in the SAP.

Descriptive statistics (e.g., means and medians) will be used to summarize the individual items and sub-scale scores of HRQOL data at each scheduled assessment time point. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized.

Detailed analysis plan will be specified in the SAP.

10.1.2.4.2. Health Economic Outcomes Analyses

EQ-5D-5L scores will be summarized by descriptive statistics.

10.1.2.5. Safety analysis

Safety will be evaluated by the incidence of AEs, causality, severity, seriousness, and type of AEs, and by evaluation of the subject's vital signs, ECOG performance status, clinical laboratory test results, ECG, and LVEF data (as clinically indicated).

A summary of study drug exposure, including total dose, duration of treatment, dose intensity, and the proportion of subjects with dose modifications will be summarized. Reasons for dose modifications will be listed by subject and summarized.

Concomitant medications will be listed by subject and will be summarized.

Safety data will be listed by subject and summarized.

10.1.2.5.1. Adverse events

Summary tables and listings for adverse events will include treatment-emergent adverse events (AEs), where treatment-emergent AE is defined as any AE that occurred between the first dose of any study drug and 28 days following the last dose of any study drug. The incidence of AEs (new or worsening from baseline) will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and/or preferred term, severity (based on NCI CTCAE v 5.0 grading as assessed by the Investigator), seriousness, and relation to study treatment. The following summaries will be produced:

- All AEs
- AEs leading to dose modifications
- Treatment-related AEs
- Grade 3 or higher AEs
- Grade 3 or higher treatment-related AEs

- The most commonly reported AEs (ie, those events reported by ≥ 10% of all subjects)
- SAEs
- Discontinuations due to AEs

By-subject listings will be provided for on-treatment deaths (on-treatment is defined as the period starting from the first dose to 28 days after the last dose), AEs, SAEs, and AEs leading to discontinuation of treatment.

10.1.2.5.2. Clinical laboratory evaluation

For laboratory tests included in the NCI CTCAE, laboratory data will be graded accordingly; a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by NCI CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, serum chemistry and coagulation studies, and urinalysis laboratory tests:

- Descriptive statistics for the actual values and/or change from baseline of clinical laboratory parameters over time.
- Shift tables using NCI CTCAE grades to compare baseline to the worst on-treatment value (for laboratory tests where NCI CTCAE grades are not defined, shift tables using the low/normal/high/[low and high] classification to compare baseline to the worst on-treatment may be generated).
- Listings of laboratory data with values flagged to show the corresponding NCI CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above-mentioned tables and listings, graphical displays of key safety parameters, such as scatter plots of actual or change in laboratory tests over time or box plots may be specified in the SAP.

10.1.2.5.3. Other Safety Data

Descriptive statistics for the actual values and/or the changes from baseline of vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) over time will be summarized.

Descriptive statistics of ECOG PS over time will be summarized by frequency. Shift tables may be provided for ECOG PS from baseline to worst value of post-baseline assessments.

Categorical analysis of QTcF intervals may be performed. Maximum QTcF intervals and maximum changes from baseline may also be summarized similarly in a separate display. ECG abnormalities if collected will be presented in a data listing.

Additional safety analyses may be performed if deemed necessary.

10.2. 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.

10.3. Pharmacokinetic Analyses

Pharmacokinetic parameters will be estimated using noncompartmental analysis methods. Descriptive statistics (ie, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum, and maximum) will be used to summarize PK parameters of ivosidenib. Such parameters may include (but are not limited to) area under the concentration-vs time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}) and trough concentration (C_{trough}).The relationships between dose and both C_{max} and AUC will be explored graphically for dose proportionality where appropriate. Descriptive statistics (i.e, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum, and maximum) will be summarized for the PK concentration data over planned time points.

The Pharmacokinetic Analysis Set will be used for summaries of PK data, as well as listings of derived parameters and concentration data for Ivosidenib.

Concentrations of ivosidenib might be used alone or combined with data from other studies for modelling activities such as population PK modelling and physiological based pharmacokinetic modelling, in order to support the development of ivosidenib.

10.3.1. Pharmacodynamic Analyses

Descriptive statistics (including but not limited to) number of subjects, mean and standard deviation will be used to summarize plasma 2-HG concentrations at different nominal time points across participants. The potential relationship between plasma exposure of ivosidenib and plasma 2-HG levels will be explored with descriptive and graphical methods as appropriate.

The pharmacodynamic analysis set will be the primary analysis set for summaries and listing of 2-HG concentrations and changes from baseline in circulating concentrations 2-HG.

Details of the PK and PD analyses will be described in a separate analysis plan.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator and the heads of the study centres will allow the monitors, the persons responsible for the audit, the representatives of the IRB, and of the Competent Authorities to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the structure mentioned in document entitled administrative part of clinical study protocol.

If on-site monitoring cannot be accomplished, remote Source Data Verification may be performed in accordance with local regulations

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

12.1.1. Before the study

The Investigator and the heads of the study centres will allow the monitor to visit the site and facilities where the study will take place to ensure compliance with the protocol requirements.

Training sessions may be organised for the Investigators and/or instruction manuals may be given to the Investigators.

12.1.2. During the study

The Investigator and the heads of the study centres will allow the monitor to:
- Review of the study site's processes and procedures.
- Verify appropriate clinical Investigator supervision of study site staff and third-party vendors.
- Inspect the site, the facilities and the material used for the study.
- Meet all members of his/her team involved in the study.
- Consult the documents relevant to the study.
- Have access to the e-CRF (*i.e.* Access to an analogic phone line or his/her computer) and/or to the e-COA service provider's database to check that they been filled out correctly.
- Check that the e-CRF and e-COA have been filled out correctly.
- Directly access source documents for comparison of data therein with the data in the electronic case report forms and/or to the e-COA service provider's database.
- Verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and / or the investigation schedule, and arranged between the Investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the Investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (*i.e.* audit trail). The Investigator will save data at regular intervals.

The Investigator and the heads of the study centres must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the Sponsor, the Investigator undertakes:

At the start of the study, to print the medical files of all participants allowing a reliable verification of the study criteria (*e.g.* Medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol).

During the study, to print in real time each data entry and each data change.

The Investigator or designated person of the site team will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the Investigator will provide all the print-outs of the medical files of the participants. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the Investigator will supply the monitor, at each visit, with a print-out of the medical files of the participants and the records of the changes made. Each print-out will be personally dated and signed, by the Investigator and the monitor on the first page. The number of pages will also be indicated by the Investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the Sponsor, the Investigator undertakes to give access to the monitor to the computerised medical files of all participants. If the monitor cannot access to the tracking of the changes made to the medical files, the Investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the participants. Each print-out will be personally dated and signed, by the Investigator and the monitor on the first page. The number of pages will also be indicated by the Investigator and the monitor on the first page.

The Investigator undertakes to keep:

- All medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the Sponsor.
- If the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the Sponsor or when the monitor cannot access to the audit trail in the computer system.

- All original source-documents (originals of specific examinations, informed consent forms, RTSM reports or equivalent document, etc.).

12.3. Audit - Inspection

The Investigator and the heads of the study centres should be informed that an audit may be carried out before, during or after the end of the study.

If on-site auditing cannot be accomplished, remote audit may be performed in accordance with local regulations.

The Investigator and the heads of the study centres should be informed that the Competent Authorities may also carry out an inspection in the facilities of the Sponsor and/or the study centre(s). The Sponsor will inform the Investigators and the heads of the study centres concerned immediately upon notification of a pending study centres inspection. Likewise, the Investigator and the heads of the study centres will inform the Sponsor of any pending inspection.

The Investigator and the heads of the study centres must allow the representatives of the Competent Authorities and persons responsible for the audit:
- To inspect the site, facilities and material used for the study.
- To meet all members of his/her team involved in the study.
- To have direct access to study data and source documents.
- To consult all the documents relevant to the study.

If the computerised medical file is considered as not validated, the Investigator and the heads of the study centres undertakes to provide all the source-documents and the print-outs of the medical files of the participants and, if the computer system used allows, the record of the changes made during the study.

If the computerised medical file is considered as validated, the Investigator and the heads of the study centres undertakes to:
- Give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerised medical files of all participants.
- Provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

12.4. Supervisory committees

Not applicable.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the Investigator's brochure, the "Participant information and consent form" document, the document describing names of the Investigator and co-Investigator(s) with the Investigator's curriculum vitae, the document indicating the anticipated payments to the study centre (including the payments to study participants), the insurance documents and other necessary documents will be submitted to (an) Institutional Review Board by the head of the study centre in accordance with local regulations.

The study must not start in a centre before the study contract has been made between the Sponsor/CRO and the study centre. Prior to the conclusion of the contract, written approval by the head of the study centre, based on a favourable opinion of the corresponding IRB(s), has been obtained, and the local regulatory requirements have been complied with.

During the study, the Investigator will submit the progress of the study in writing to the IRB that has examined the study conduct, via the head of study centre, once a year and upon request of the IRB for review of whether the study can be continued in accordance with local regulations.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (Appendix 1) well as ICH E6, the Ministry of Health, Labour and Welfare Ordinance No. 28 (Ordinance for GCP) and related local regulation and the clinical study protocol.

13.3. Participant information and informed consent

The Investigator, in collaboration with the Sponsor parties, should prepare the information and consent forms (ICFs) in clear and simple Japanese language in accordance with Japan's GCP standards. The Investigator-prepared ICFs must be subject to the Institutional Review Board review and approved by the Investigational Review Board, and subsequently by the head of the study centre beforehand.

The Investigator or a person designated by him/her is required to collect written consent from each participant before his/her participation in the study. Prior to this, the Investigator or his/her delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs. The participant must be informed that he/she has the possibility not to participate in the study and that he/she is free to reconsider his/her consent at any time

The participant will be provided with an information and consent form in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

One, or two if required by local regulation, original information and consent form(s)must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.

If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion. The participant must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent. In the case where the Investigator-designated clinical study collaborator has provided supplementary explanation, he/she should sign and date the form as well.

The participant will be given one signed copy (or original if required by local regulation) of the information and consent form. A signed original will be kept by the Investigator.

A copy of the information and consent form in the language(s) of the country is given in the "Participant information and consent form" document attached to the protocol.

13.4. Modification of the information and consent form

Whenever important new information, which may be relevant to the consent of the subjects participating in the study, becomes available, the Investigator should explain it to each subject promptly and then check whether or not the subject has intention to continue participating in the study. The subject's intention as well as the fact that the new information was provided to the subject should be documented in the medical file.

Furthermore, if the Investigator deems amendment to the ICF necessary based on the new information, he/she should promptly amend it in collaboration with the Sponsor and following its validation. If the Sponsor considers the amendment of ICF is necessary, they ask the Investigator to amend the ICF with the draft document. Such amendments may only be implemented after written approval of the IRB and subsequent approval of the head of the study center.

Such revisions may only be implemented after written approval of the IRB and subsequent approval of the head of the study centre have been obtained with the exception of a revision required to eliminate an immediate hazard to the study participants.

Each subject and his/her impartial witness (if any) affected by the amendment must date and sign the new version of the ICF together with the Investigator who conducted the informed consent discussion. In the case where the Investigator-designated clinical study collaborator has provided supplementary explanation, he/she should sign and date the form as well.

The subject will receive a copy of the signed and dated new version of the ICF, and the original will be kept in the subject's medical file.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

A 21 CFR Part 11-compliant electronic data capture system will be used in this study. An electronic case report form (e-CRF) is designed to record the data required by the protocol and collected by the Investigator.

The e-CRF will be produced by I.R.I.S. in compliance with its specifications. The Investigator or a designated person from his/her team will be trained for the use of the e-CRF by the Sponsor, or the CRO.

Data entry at the Investigator's site will be performed by the Investigator or by the designated person from his/her team after completion of the participant's Medical File.

The Investigator or the designated person from his/her team agrees to complete the e-CRF, at each participant visit, and all other documents provided by the Sponsor (e.g. documents relating to the IMP management…).

Data recorded directly on e-CRF and considered as source data (see Section 4.5) must be collected immediately in the e-CRF. The other e-CRF forms must be completed as soon as possible following each visit.

All corrections of data on the e-CRF must be made by the Investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of the audit trail feature of the eCRF including date, reason for modification and identification of the person who has made the change.

To ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the Investigator's sites, the Sponsor or third parties.

Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the Investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However, the Investigator has the possibility to modify a data if deemed necessary via a request to the Sponsor.

The Investigator or authorised member for sign-off must confirm the authenticity of the data recorded in the e-CRF by signing-off the e-CRF in a timely manner as defined in the e-CRF guide.

14.2. Data management

All data for participants recruited for the trial will be entered onto the e-CRFs via an electronic data capture (EDC) system provided by the Sponsor. Only authorised staff may enter data onto the e-CRFs. If an entry error is made, the corrections to the e-CRFs will be made according to e-CRF guidelines by an authorised member of the site staff. Any discrepancies will be noted in the e-CRF system by means of electronic data queries. Authorised site staff will be asked to respond to all electronic queries according to the e-CRF guidelines. Access to the EDC system will be controlled, and a complete audit trail of all data changes will be maintained.

In case of data generated by PK/ADA laboratory, Independent Radiology Center, and e-COA service provider's, the Providers provide electronic transfer of computerised data to Sponsor according to transfer specifications.

All data collected are stored in a secured database. This database is locked, unblinded if applicable and made available for statistical analysis at the end of the study or in case of interim analysis.

14.3. Archiving

The Investigator and a record retainer assigned by the head of the study centre will keep all information relevant to the study for at least 25 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the Investigator or an authorized member of his/her team will download an electronic copy of each participant's data from the e-CRF and should keep it in a reliable, secure and durable location. The file includes all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

All data reported in e-COA will be provided to the Investigator's site.

The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage or deterioration for the duration of the archiving period.

15. INSURANCE

I.R.I.S., the Sponsor of the study, is insured under the liability insurance program subscribed by Les Laboratoires Servier to cover its liability as the Sponsor of clinical studies on a worldwide basis.

Nihon Servier, the in-country caretaker of this study, is insured locally under the comprehensive general liability insurance program to cover clinical study risk with endorsement for no fault for compensation insurance for clinical studies.

Nihon Servier is primarily responsible for dealing with the damages and compensation for study-related injuries in Japan. If a subject participating in the study suffers health injuries related to the study, except for cases caused by the subject's wilful action, medical fees and medical allowances will be appropriately compensated in accordance with "The Guideline on Compensation for Injury Resulting from Participation in Clinical Trials" issued by Japan Pharmaceutical Industry Legal Affairs Association on March 16, 1999.

The document describing an outline of the compensation system of Nihon Servier will be provided to the study centre separately.

Furthermore, Nihon Servier, on behalf of the Sponsor, will subsidize transportation fees, etc. for study visits of subjects, via the study centre, in order to reduce the burden of subjects participating in the study. The amount of the subsidy per visit, how to transfer it to the subjects, etc., will be discussed and agreed with the study centre. The payment scheme must be approved by the Institutional Review Board before the initiation of the study.

16. OWNERSHIP OF THE RESULTS – DATA SHARING POLICY AND PUBLICATION POLICY

I.R.I.S., acting as the study Sponsor, assumes full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

I.R.I.S. will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalisation of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to the Sponsor in accordance with the guidelines set forth in the applicable publication policy or financial agreement.

The Investigator, who submitted the project, shall take the Sponsor's comments into due consideration.

As the study is a multicentre one, the first publication must be performed only with data collected from several study sites and analysed under the responsibility of I.R.I.S. The Investigator commits himself not to publishing or communicating data collected in only one centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other Investigators and I.R.I.S. has been provided.

Data Sharing Policy is available at https://clinicaltrials.servier.com/data-request-portal/. Researchers can ask for a study protocol, participant-level and/or study-level clinical trial data including clinical study report.

They can ask for all interventional clinical studies:
- submitted for new medicines and new indications approved after 1 January 2014 in the European Economic Area (EEA) or the US.
- Where Servier or an affiliate are the Marketing Authorization Holders. The date of the first Marketing Authorization of the new medicine (or the new indication) in one of the EEA Member States will be considered within this scope.

In addition, Servier’s data sharing policy includes all interventional clinical studies in participants:
- Sponsored by Servier.
- With a first participant enrolled as of 1 January 2004 onwards.
- For New Chemical Entity or New Biological Entity (new pharmaceutical form excluded) for which development has been terminated before any marketing authorization approval.

The datasets generated and/or analysed during the current study will be available upon request from www.clinicaltrials.servier.com after the Marketing Authorisation has been granted.

Summary results and a lay summary will be published on clinicaltrials.servier.com within 12 months after the end of the study.

The results will be submitted for publication in scientific literature within 18 months after the end of the study.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the Sponsor and the Investigator

17.1.1. Persons to inform

In accordance with local regulations, the Investigator and/or the Sponsor (including in-country caretaker) will inform, the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

With the agreement of the participant, the Investigator will inform the participant's general practitioner about his/her participant's participation in a clinical study.

17.1.2. Protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or amendment must be discussed and approved by Investigator and the Sponsor.

All protocol amendments must be drafted in accordance with the Sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All amendments must be submitted by the Sponsor, in accordance with local regulations, to the head of the centre for review by or report to the IRB that examined the initial protocol. They can only be implemented after written approval of the head of the centre, based on a favourable opinion of the IRB, has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, except for a measure required to eliminate an immediate risk to the study participants.

Furthermore, amended protocol are to be submitted to the competent authorities in accordance with local regulations.

17.1.3. Final study report

The study report(s) will be drafted by Biostatistics - Centre of Excellence Methodology and Valorisation of Data of I.R.I.S. in compliance with I.R.I.S. standard operating procedure.

17.2. Concerning the Sponsor

The Sponsor undertakes to:

- Supply the Investigator and the head of the study centre with adequate and sufficient information concerning the IMP administered during the study to enable him/her to carry out the study.
- Supply the Investigator and the head of the study centre with the Product Information.
- Supply the Investigator and the head of the study centre with the Investigator's Brochure, the one best suited to ensure participant safety, and any potential updated version during the study:
  - For the IMP if marketed, to be appended to Investigator's Brochure (Section 4. Guidance for the Investigator).
  - For all reference products used in the study.
- Obtain any authorisation to perform the study and/or import licence for the IMPs administered that may be required by the local authorities before the beginning of the study.
- Take all the necessary precautions to maintain the safety of the processed data, in particular their confidentiality, their integrity and their availability, by assessing risks identified concerning personal data protection. The following measures will be implemented (non-exhaustive):
  - Management of authorisation to access to personal data (e-CRF).
  - Identification and authentication measures before accessing personal data (e-CRF).
  - Traceability measures for the access to and modification of personal data (e-CRF).
  - Secured data transfer.
  - Time limit for storing personal data.
- Handle any security breach by implementing an internal committee (including CISO, DPO, communication department…) in order to qualify the security incident (Information systems, nature and number of personal data impacted), to define an action plan for corrective actions and to notify to relevant person (authority and/or if needed individuals).

17.3. Concerning the Investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the Investigator by the Sponsor with respect to the IMP and the study are strictly confidential.

The Investigator expressly agrees that data on his/her professional and clinical experience is collected by the Sponsor on paper and computer and stored for its sole use relating to its activities as the Sponsor of clinical trials, in accordance with GCP.

He/she has a right to access, modify, and delete his/her own personal data by applying to the Sponsor.

In case participant wants to exercise his/her rights regarding personal data protection, he/she will contact the Investigator. The Investigator will forward the request to the Sponsor (Appendix 4).

The Investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the Sponsor. The clinical study protocol given to the Investigator may be used by him/her or his/her colleagues to obtain the informed consent of study participants. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the Sponsor.

The Investigator must not disclose any information without the prior written consent from I.R.I.S., except to the representatives of the Competent Authorities, and only at their request. In the latter case, the Investigator commits himself/herself to informing I.R.I.S. prior to disclosure of information to these authorities.

A participant screening log and a full identification and enrolment list of each participant will be completed and kept in a safe place by the Investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The participant screening log must be completed from the moment the Investigator checks that a participant could potentially take part in the study (by assessment of participant medical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the Investigator delegates under his/her responsibility a part of the follow-up of the study (co-Investigator, nurse…) and any other person involved in the study for this centre (cardiologist, pharmacist…) must figure in the "Organisation of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the site.

17.3.3. Documentation supplied to the Sponsor

The Investigator undertakes before the study begins:

- To provide his/her dated and signed English and Japanese Curriculum Vitae (CV) to the Sponsor, together with that of his/her co-Investigator(s).
- To provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured.
- To provide any other document required by local regulation.

The CV of other members of the team involved in the study (if possible, in English) will be collected during the course of the study (at least, members involved in the participants' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

17.3.4. Serious Breach

A serious breach is defined as any deviation of the approved protocol version or the clinical trial regulation that is likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial. The Investigator should ensure that the study site staff is able to identify the occurrence of a suspected serious breach and that any suspected serious breach is promptly reported to the Sponsor or delegated party (contact point designated by the Sponsor).

18. REFERENCES

ACS. 2019. 'Survival rates for bile duct cancer', American Cancer Society, Accessed 05 December 2019. https://www.cancer.org/cancer/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html.

ACS. 2021. 'Cancer Facts & Figures 2021'. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2021.html.

Agency, European Medicines. 2018. "Question and answer on adjustment for cross-over in estimating effects in oncology trials." In.

Brieau B, Dahan L, De Rycke Y, Boussaha T, Vasseur P, Tougeron D, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: A large multicenter study by the Association des Gastro-Enterologues Oncologues. Cancer. 2015;121(18):3290-7. [PE0162864]

Chowdhury R, Yeoh KK, Tian YM, Hillringhaus L, Bagg EA, Rose NR, et al. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. EMBO Rep. 2011;12(5):463-9. [PE0163011]

Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009;462(7274):739-44. [PE0162691]

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. [PE0068306]

Figueroa, M. E., O. Abdel-Wahab, C. Lu, P. S. Ward, J. Patel, A. Shih, Y. Li, N. Bhagwat, A. Vasanthakumar, H. F. Fernandez, M. S. Tallman, Z. Sun, K. Wolniak, J. K. Peeters, W. Liu, S. E. Choe, V. R. Fantin, E. Paietta, B. Lowenberg, J. D. Licht, L. A. Godley, R. Delwel, P. J. Valk, C. B. Thompson, R. L. Levine, and A. Melnick. 2010. 'Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation', Cancer Cell, 18: 553-67.[PE0162695]

Geisbrecht BV, and Gould SJ. The human PICD gene encodes a cytoplasmic and peroxisomal NADP(+)-dependent isocitrate dehydrogenase. J Biol Chem. 1999;274(43):30527-33. [PE0163120]

Gross S, Cairns RA, Minden MD, Driggers EM, Bittinger MA, Jang HG, et al. Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. J Exp Med. 2010;207(2):339-44. [PE0163134]

Kim BJ, Yoo C, Kim KP, Hyung J, Park SJ, Ryoo BY, and Chang HM. 'Efficacy of fluoropyrimidine-based chemotherapy in patients with advanced biliary tract cancer after failure of gemcitabine plus cisplatin: retrospective analysis of 321 patients', Br J Cancer, 2017,116:561-67. [PE0163261]

Koivunen P, Lee S, Duncan CG, Lopez G, Lu G, Ramkissoon S, et al. Transformation by the (R)-enantiomer of 2-hydroxyglutarate linked to EGLN activation. Nature. 2012;483(7390):484-8. [PE0163266]

Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW, and Group Advanced Biliary Cancer Working. 'Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial', Lancet Oncol, 2021,22:690-701. [PE0165118]1

Linda H, von Heijne A. A case of posterior reversible encephalopathy syndrome associated with gilenya (fingolimod) treatment for multiple sclerosis. Frontiers in Neurology. 2015;6:39. [PE0166771]

Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature. 2012;483(7390):474-8. [PE0163350]

Matsuda, Tomohiro, and Kumiko Saika. "Cancer burden in Japan based on the latest cancer statistics: need for evidence-based cancer control programs." Ann Cancer Epidemiol 2.2 (2018).

Matsuyama Ryusei, Daisuke Morioka, Ryutaro Mori, Seigo Hiratani, Yasuhiro Yabushita, Yohei Ota, Takafumi Kumamoto, Koichi Taniguchi, and Itaru Endo. , 2018,81:949-55. [PE0163399]

Oh DY, Lee KH, Lee DW, Yoon J, Kim TY, Bang JH, Nam AR, Oh KS, Kim JM, Lee Y, Guthrie V, McCoon P, Li W, Wu S, Zhang Q, Rebelatto MC, and Kim JW. 'Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study', Lancet Gastroenterol Hepatol, 2022,7:522-32. [PE0171682]

Okawa Y; Ebata N; Kim NKD; Fujita M; Maejima K; Sasagawa S; Nakamura T; Park WY; Hirano S; Nakagawa H. Actionability evaluation of biliary tract cancer by genome transcriptome analysis and Asian cancer knowledgebase. Oncotarget. 2021; 12(15):1540-1552. [PE0171895]

Rizzo Alessandro, Angela Dalia Ricci, and Giovanni Brandi. 'IDH inhibitors in advanced cholangiocarcinoma: Another arrow in the quiver?', Cancer Treatment and Research Communications, 2021,27:100356. [PE0161917]

Saha SK, Parachoniak CA, Ghanta KS, Fitamant J, Ross KN, Najem MS, et al. Mutant IDH inhibits HNF-4alpha to block hepatocyte differentiation and promote biliary cancer. Nature. 2014;513(7516):110-4. [PE0163621]

Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature. 2012;483(7390):479-83. [PE0163021]

Van Dyke AL, Shiels MS, Jones GS, Pfeiffer RM, Petrick JL, Beebe-Dimmer JL, and Koshiol J. 'Biliary tract cancer incidence and trends in the United States by demographic group, 1999-2013', Cancer, 2019,125:1489-98. [PE0163638]

Wang F, Travins J, DeLaBarre B, Penard-Lacronique V, Schalm S, Hansen E, et al. Targeted Inhibition of Mutant IDH2 in Leukemia Cells Induces Cellular Differentiation. Science. 2013;In press. [PE0163639]

Ward PS, Patel J, Wise DR, Abdel-Wahab O, Bennett BD, Coller HA, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell. 2010;17(3):225-34. [PE0162991]

Welch JS, Ley TJ, Link DC, Miller CA, Larson DE, Koboldt DC, et al. The origin and evolution of mutations in acute myeloid leukemia. Cell. 2012;150(2):264-78. [PE0162987]

Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell. 2011;19(1):17-30. [PE0162978]

Yen KE, Bittinger MA, Su SM, and Fantin VR. Cancer-associated IDH mutations: biomarker and therapeutic opportunities. Oncogene. 2010;29(49):6409-17. [PE0162971]

Ying Jie, and Chen Jinfei. 'Combination versus mono-therapy as salvage treatment for advanced biliary tract cancer: A comprehensive meta-analysis of published data', Critical reviews in oncology/hematology, 2019,139:134-42. [PE0162968]

Yoshihara T, Hamamoto T, Munakata R, Tajiri R, Ohsumi M, and Yokota S. Localization of cytosolic NADP-dependent isocitrate dehydrogenase in the peroxisomes of rat liver cells: biochemical and immunocytochemical studies. J Histochem Cytochem. 2001;49(9):1123-31. [PE0162966]

19. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Patient performance status

Not applicable since nonsubstantial amendment #1 was implemented.

Appendix 3: New Response Evaluation Criteria in Solid Tumors: Revised RECIST guideline (version 1.1), Eisenhauer, 2009

Measurability of tumor at baseline

At baseline, tumor lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT-scan (CT-scan slice thickness no greater than 5 mm),
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable),
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT-scan (CT-scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET-scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions,
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above,
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts,
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.
Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions
When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).
Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.
A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.* 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT-scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default

value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions
This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.
Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis).
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease
The concept of progression of non-target disease requires additional explanation as follows:
When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.
When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: *i.e.* an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: *i.e.* not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET (a 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image) at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1: Time point response: patients with target (± non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = Not evaluable

When patients have non-measurable disease only (therefore non-target), Table 2 is to be used.

Table 2: Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	on-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = Not evaluable.

1 = Non-CR/non-PD' is preferred over stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response **is not** required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second

and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response **is** required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3: Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = Not evaluable.

1 = If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.
For equivocal findings of progression (*e.g.* very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of tumor re-evaluation
Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (*e.g.* time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

Confirmatory measurement/duration of response

Confirmation
In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, *i.e.* in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response
The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).
The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease
Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).
The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.
Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Appendix 4: Instructions to Investigator for handling data rights requests

DATA PROTECTION / GDPR (General Data Protection Regulation of 27 April 2016 n°2016/679)

INSTRUCTIONS TO INVESTIGATOR FOR HANDLING DATA RIGHTS REQUESTS

In the framework of a research study/clinical trial, a participant to the study may exercise his/her rights, i.e. may ask IRIS (as data controller) for:

- access to his/her data
- rectification of inaccurate/incomplete information
- restriction of processing of data
- objection to processing of data
- data portability (receiving his/her data in a readable format)

In accordance with the Informed Consent Form and information notice provided to participant, we requested participant to contact you first for exercising their rights.
Request for exercise of rights:

- has to be a **written** one (either originating from an (e)-mail from a participant or from request expressed orally to you and put in written)
- has to be sent **by you** by e-mail or by mail **to** IRIS (as data controller) to central address dataprivacy@servier.com or local Servier address as mentioned in ICF/information notice provided/available

DO **Instructions to be followed by you**	**DON'T** **What you should not do**
E-mail title: Data protection rights	Do not forward participant e-mail (if applicable)
Study name/number	
Participant number	**No information regarding participant identity**: No participant's name, e-mail address, participant's signature
As soon as possible without exceeding a week	

IRIS and INVESTIGATOR responsibilities

GDPR requirement:
It is mandatory for IRIS as data controller to provide an answer to participant/volunteer within 1 month following the request (article 12 of GDPR)
Clinical trials requirements:
It is prohibited for IRIS as a Sponsor to know the identity of the participants/volunteer participating to studies

	IRIS responsibility	Investigator responsibility
Forward/inform IRIS of the request		YES
Timelines	Answer within 1 month once expressed by the participant	Request: transmitted to IRIS as soon as expressed by the participant Answer: transmitted by you to participant as soon as sent by IRIS
Answer the request	YES	

Appendix 5: Eastern Cooperative Oncology Group Performance Status Scoring

Grade	Symptomatology
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-655.

Appendix 6: Prohibited Concomitant Medications

Prohibited medications and certain foods are not allowed in this study while subjects are receiving study drug.	
Strong CYP3A Inducers	**CYP3A Substrates with a Narrow Therapeutic Window**
Avasimibe, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, rifabutin, St. John's wort	Alfentanil, astemizole[1], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, everolimus, sirolimus, tacrolimus, terfenadine[1]

Note that this is not an exhaustive list. For an updated list, see the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm

"CYP substrates with a narrow therapeutic window" refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

1 Withdrawn from the United States market because of safety reasons.

Appendix 7: New York Heart Association Classification

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix 8: Fridericia's Formula

$QTcF = QT/RR^{1/3}$

Appendix 9: Medications Known to Prolong the QT Interval

amiodarone	dofetilide	grepafloxacin	moxifloxacin	quinidine
astemizole	dolasetron	halofantrine	norfloxacin	sevoflurane
azithromycin	domperidone	haloperidol	ofloxacin	sotalol
bepridil	droperidol	ibutilide	ondansetron	sparfloxacin
chloroquine	erythromycin	itraconazole	palonosetron	terfenadine
chlorpromazine	escitalopram	ketoconazole	pentamidine	thioridazine
ciprofloxacin	flecainide	levofloxacin	pimozide	voriconazole
citalopram	gatifloxacin	levomethadyl	posaconazole	
clarithromycin	gemifloxacin	mesoridazine	probucol	
disopyramide	granisetron	methadone	procainamide	

For a complete and updated (ongoing) list of medications, please use the following link:
https://crediblemeds.org/healthcare-providers/

Appendix 10: Examples of Strong and Moderate CYP3A4 Inhibitors

Moderate CYP3A4 Inhibitors
Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
Strong CYP3A4 Inhibitors
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole
Ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole
Ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

Note: Based on FDA guidelines; Investigators should follow local institutional guidelines, where appropriate.

Appendix 11: Representative Examples of Low-Fat and High-Fat, High-Calorie Meals

Low-fat breakfast:

A) 2 slices of white bread toast, 1 tablespoon light fat margarine, 1 tablespoon of jelly, and 8 ounces of skim milk (319 calories and 8.2 grams of fat).

B) 1 cup of cereal, 1 slice of toast with jam, 8 ounces of skim milk, and 1 cup of decaffeinated coffee or tea (520 calories and 2 grams of fat).

A high-fat breakfast consists of the following and may be adapted to the local regional preference: 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk. This representative high-fat breakfast contains approximately 1000 calories and 58 grams of fat.