Official Title: Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine Cisplatin Chemotherapy as First-Line Treatment of Patients with Advance Cholangiocarcinoma Harboring FGFR2 Gene Rearrangements

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A Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring *FGFR2* Gene Rearrangements

FOENIX-CCA3

Protocol Number: TAS-120-301

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This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

CONFIDENTIAL

SUMMARY OF PROTOCOL AMENDMENTS

The original protocol for Study TAS-120-301 was approved on 13 September 2019; this document is Amendment 1, issued 29 January 2020. Apart from updates to the document date and headers, a total of 2 changes were made in this amendment:

1. An erroneous EudraCT number on the cover page was corrected; and
2. The requirement that phosphorus be assessed on Day 4 of Cycle 1 was removed from Table 1 (Schedule of Events) and throughout the protocol (the schedule for all other chemistry assessments remains the same as in the original version).

No other changes, including editorial changes, were made to the document.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Taiho Pharmaceutical Co., Ltd. and Taiho Oncology, Inc.	**Name of Investigational Product:** Futibatinib (TAS-120)	
Title of Study: **FOENIX-CCA3:** A Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring *FGFR2* Gene Rearrangements		
Phase of Development: Phase 3	**Countries:** Global	**Estimated Number of Sites:** 175

Study Rationale:

Aberrations in fibroblast growth factor (FGF) or the FGF receptor (FGFR) are a reported genetic modification in cholangiocarcinoma (CCA); in particular, *FGFR2* gene rearrangements, including gene fusions, have been identified as an early driver of oncogenic events in approximately 15% of CCA patients. Futibatinib (TAS-120), an oral, highly selective, irreversible tyrosine kinase inhibitor (TKI) that inhibits both mutant and wild-type FGFR1-4 isoforms, has shown promising antitumor activity in preclinical studies against a variety of tumor cell lines or tumor models harboring FGFR aberrations. In an ongoing Phase 1/2 clinical study (Study TAS-120-101), treatment with futibatinib resulted in further evidence of efficacy.

The Phase 3 study described in this protocol will evaluate the efficacy and safety of futibatinib against that of the current standard of care (gemcitabine-cisplatin chemotherapy) in the first-line treatment of patients with locally advanced, metastatic, or recurrent unresectable intrahepatic CCA (iCCA) harboring *FGFR2* gene rearrangements.

Objectives and Endpoints:

The objectives of this study are to compare the following endpoints in patients with locally advanced, metastatic, or recurrent unresectable iCCA harboring *FGFR2* gene rearrangements, who are treated with either futibatinib monotherapy or gemcitabine-cisplatin chemotherapy:

Primary

- Progression-free survival (PFS) by independent central review (ICR), based on Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1)

Secondary

- Objective response rate (ORR)
- Disease control rate (DCR)
- Overall survival (OS)
- PFS according to Investigator assessment of radiologic images
- Safety and tolerability

Exploratory

- PFS on next-line therapy (PFS2)
- Duration of response (DOR)
- Patient-reported outcomes (PRO)
- To assess the population pharmacokinetics (Pop PK) of futibatinib and to explore the relationship between PK and efficacy or toxicity.

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STUDY DESIGN AND POPULATION

Study Design:

Study TAS-120-301 is an open-label, multinational, parallel 2-arm, randomized Phase 3 study evaluating the efficacy and safety of futibatinib versus gemcitabine-cisplatin chemotherapy as first-line treatment of patients with advanced, metastatic, or recurrent unresectable iCCA harboring *FGFR2* gene rearrangements. Eligible patients will be randomized on a 1:1 basis to the following study arms:

- **Experimental Arm:** Patients will receive futibatinib at an oral dose of 20 mg, administered daily (QD) on every day of a 21-day cycle.
- **Control Arm:** On Days 1 and 8 of a 21-day cycle, patients will receive:
  - Cisplatin 25 mg/m^2 in 1000 mL 0.9% saline by intravenous (I.V.) infusion over 1 hour, followed by 500 mL 0.9% saline over 30 minutes; and
  - Gemcitabine 1000 mg/m^2 in 250-500 mL 0.9% saline by I.V. infusion over 30 minutes, beginning after completion of the cisplatin and saline infusions.

Patients in the Experimental Arm may continue to receive continuous futibatinib until documentation of progressive disease (PD) per RECIST 1.1, or until other withdrawal criteria are met, whichever comes first. However, treatment may continue following PD per RECIST 1.1 if the patient is clinically stable and is considered by the Investigator to be deriving continued clinical benefit from futibatinib.

Patients in the Control Arm may receive gemcitabine-cisplatin chemotherapy for up to 8 cycles or until PD or other withdrawal criteria are met, whichever comes first. Patients who discontinue gemcitabine-cisplatin due to documented disease progression (by ICR) may receive treatment with futibatinib ("crossover"), if medically appropriate in the opinion of the Investigator and if criteria for futibatinib treatment are met.

Randomization / Stratification Factors:

Randomization will be stratified by the following factors:

- Prior surgical excision of the primary tumor (yes vs. no);
- Geographic region (Asia vs. rest of the world); and
- Locally advanced vs. metastatic disease.

Number of Patients:

Approximately 216 patients with iCCA harboring centrally confirmed *FGFR2* gene rearrangements will be randomized.

Inclusion/Exclusion Criteria:

Inclusion:

A patient must meet all of the following inclusion criteria to be eligible for enrollment in this study:

1. Provide written informed consent.
2. Is ≥18 years of age (or meets the country's regulatory definition for legal adult age).
3. The patient has histologically confirmed, locally advanced, or metastatic, or recurrent unresectable iCCA harboring FGFR2 gene rearrangements based on testing performed by the designated central laboratory.
4. Patient has radiographically measurable disease per RECIST 1.1.

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5. Patients who have received treatment for locally advanced disease (for example, trans-arterial chemoembolization, selective internal radiation therapy, external beam radiation) must have evidence of radiographic progression with measurable disease outside the previously-treated lesions.
6. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.
7. Adequate organ function as defined by the following criteria:
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 ×upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5 × ULN.
   - Total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN for patients with Gilbert's syndrome.
   - White Blood Count (WBC) ≥ 2000/mm^3 (≥ 2.0 × 10^9/L)
   - Absolute neutrophil count (ANC) ≥ 1000/mm^3 (ie, ≥ 1.0 × 10^9/L by International Units [IU])
   - Platelet count ≥ 100,000/mm^3 (IU: ≥ 100 × 10^9/L)
   - Hemoglobin ≥ 9.0 g/dL
   - Phosphorus ≤ 1.5 × ULN
   - Creatinine clearance: ≥ 60 mL/min
8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test within 7 days prior to administration of the first dose of futibatinib. Female patients are not considered to be of child-bearing potential if they have a history of hysterectomy or are post-menopausal defined as no menses for 12 months without an alternative medical cause. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 3 months after the last dose.
9. Willing and able to comply with scheduled visits and study procedures.

Exclusion:

A patient will be excluded from this study if any of the following criteria are met:

1. Patient has received previous systemic anticancer therapy.
   - Patients receiving adjuvant or neoadjuvant treatment and completed ≥6 months prior to randomization are eligible.
2. Patient has mixed hepatocellular carcinoma – iCCA disease.
3. History and/or current evidence of any of the following disorders:
   - Non-tumor related alteration of calcium-phosphorus homeostasis that is clinically significant in the opinion of the Investigator.
   - Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator.
   - Retinal disorder confirmed by retinal examination and considered clinically significant in the opinion of the ophthalmologist.
4. History or current evidence of uncontrolled ventricular arrhythmias
5. Fridericia's corrected QT interval (QTcF) > 470 ms on electrocardiogram (ECG) conducted during Screening.
6. Treatment with any of the following within the specified time frame prior to the first dose of study therapy, or failure to recover from side effects of these prior therapies:
   - Major surgery within the previous 4 weeks (the surgical incision should be fully healed prior to the first dose of study therapy).
   - Radiotherapy (any dose) for extended field within 4 weeks or limited field radiotherapy within 2 weeks, and/or has not recovered from acute impact of radiotherapy.

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- Patients with locoregional therapy, eg, transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT) or ablation within 4 weeks.
- Any history of liver transplant.

7. A serious illness or medical condition(s) including, but not limited to, the following:
   - Brain metastases that are untreated or clinically or radiologically unstable (that is, have been stable for <1 month).
   - Known acute systemic infection.
   - Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months.
   - Chronic nausea, vomiting, or diarrhea considered to be clinically significant in the opinion of the Investigator.
   - Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death.
   - Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the judgment of the Investigator would make the patient inappropriate for entry into this study.
8. Patients with a history of another primary malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen in the opinion of the investigator.
9. Pregnant or breast-feeding female.
10. The patient is unable to take oral medication.

EVALUATION CRITERIA

Efficacy:

Measurements of disease will be performed throughout study treatment using RECIST guidelines (version 1.1, 2009). Radiographic tumor assessments (computed tomography [CT] or magnetic resonance imaging [MRI]) will be performed at baseline and at the end of every 2 cycles (±7 days) up to Cycle 4 (or as clinically indicated). Following Cycle 4, scans will be performed after every 3 cycles (± 7 days) or as clinically indicated, and at study completion. Efficacy endpoints will be as follows:

- **PFS per central assessment (primary):** defined as the time from date of randomization to the date of documentation of disease progression by ICR, or date of death, whichever occurs first.
- **ORR (secondary):** defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR) (per RECIST 1.1), based on ICR.
- **DCR (secondary)**: defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR (per RECIST 1.1), based on central assessment of radiologic images.
- **OS (secondary)**: measured from the date of randomization until the date of death due to any cause.
- **PFS per Investigator assessment (secondary)**: defined as the time from date of randomization to the date of disease progression based on Investigator assessment of radiographic images or death, whichever occurs first.
- **DOR (exploratory)**: defined as the time from the first documentation of response (per RECIST 1.1 and based on central assessment of radiologic images) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first.
- **PFS2 (exploratory):** defined as the time from randomization to subsequent disease progression per Investigator assessment after initiation of next-line therapy or death from any cause (whichever occurs first).

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Safety:

The assessment of safety will be based on the incidence of treatment-emergent (TE) adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose interruption, modification, and deaths. Additional safety assessments include clinical laboratory tests, vital signs, and 12-lead ECG. Grading of TEAEs will be performed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0).

Patient-Reported Outcomes:

PRO will be assessed using:

- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) is an integrated system for assessing the health-related quality of life (QoL) of cancer patients participating in international clinical trials.
- The EORTC QLQ-BIL21 is a validated tool for the assessment of QoL in patients with CCA and cancer of the gallbladder.

Pharmacokinetics:

Blood samples for Pop PK analysis will be obtained from all patients receiving futibatinib (including crossover patients) on Cycle 2, Day 1, pre-dose (from -30 min to just before dose) and at 1 hour and 3 hours (±30 min) post-dose.

Pharmacodynamics:

Blood samples will be collected for measurement of circulating tumor marker CA19-9 during screening and in conjunction with tumor assessments/scans throughout the study. In addition, circulating tumor DNA (ctDNA) will be collected to assess FGF/FGFR aberrations at screening and at the end of therapy. For patients who cross-over from the Control to the Experimental Arm, an additional ctDNA sample will be collected at the end of futibatinib therapy. Samples, or a subset of samples, will be used to assess comparability of FGFR test results to tumor tissue results and verify utility of ctDNA as an alternative to tumor biopsy as a matrix for the potential companion diagnostics.

STATISTICAL METHODS

Sample Size Determination:

Assuming median PFS of 6 months in the Control Arm and 10 months in the Experimental Arm, a total of 162 PFS events will be needed to detect a hazard ratio of 0.60 with 90% power at a 2-sided alpha level of 0.05.

Considering an enrollment rate of 4 patients per month in the first 10 months and 8 patients per month from Month 11 to Month 32, approximately 216 patients are planned to be randomized in 1:1 ratio to the Experimental Arm and Control Arm. It is estimated that 162 PFS events would occur approximately 40 months (32-month enrollment period and 8-month follow up period) after the first patient randomized. These calculations further assume a 10% loss to follow-up annually.

Name of Sponsor/Company:	**Name of Investigational Product:**
Taiho Pharmaceutical Co., Ltd. and Taiho Oncology, Inc.	Futibatinib (TAS-120)

Title of Study:

FOENIX-CCA3: A Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring *FGFR2* Gene Rearrangements

Primary Statistical Analysis (Efficacy):

Comparison of PFS (per ICR) between arms will be performed when at least 162 PFS events have been observed. The comparison will test the null hypothesis:

H_0: PFS in experimental arm = PFS in control arm,

against the alternative hypothesis:

H_1: PFS in experimental arm $\neq$ PFS in control arm.

The difference in PFS will be compared by stratified log-rank test at 2-sided α=0.05. The tests will be by the stratification factors used in the randomization. The hazard ratio and the corresponding 95% confidence intervals (CIs) will be estimated using the Cox regression model stratified by the same stratification factors. The median PFS, and the PFS rates at 6, 12 and 18 months, will be calculated using the Kaplan-Meier (KM) product-limit estimates for each treatment arm, and presented with 2-sided 95% CIs. The KM estimates of PFS will be plotted over time. The PFS censoring rules and definition of progression date will follow the Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)."

Secondary Statistical Analyses (Efficacy):

The fixed sequence procedure will be used to control the overall type I error rate of analyses for the secondary endpoints at $\alpha = 0.05$ (2-sided) after the superiority for primary efficacy endpoint, PFS, is declared. The order of testing for secondary endpoints will follow the order that they are presented below.

In the ordered sequence, each secondary endpoint will be tested at the 5% level until the first nonsignificant outcome occurs. If the first nonsignificant outcome occurs, then the results of the analysis of the subsequent endpoints will be presented for descriptive purposes only.

1. ORR

ORR will be calculated for each treatment arm with exact 95% CIs using the method of Clopper and Pearson. The analysis of ORR for comparison between treatment arms will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by the stratification factors used in the randomization.

2. DCR

DCR will be calculated for each treatment arm with exact 95% CIs using the method of Clopper and Pearson. The analysis of DCR for comparison between treatment arms will be performed using the CMH test stratified by the stratification factors used in the randomization.

3. OS

OS will be evaluated using KM estimates and the comparison in OS between the two arms will use a stratified log-rank test with the randomization stratification factors. The corresponding estimate of the hazard ratio (HR) calculated from Cox proportional hazard model with treatment group as a factor and stratified by the randomization stratification factors will be presented with a 2-sided 95% CI.

No multiplicity adjustments will be used for other secondary efficacy endpoints.

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Safety Analyses: The safety analysis will be performed in all treated patients. Descriptive statistics of safety will be presented using NCI-CTCAE v. 5.0 by treatment arm. AEs, drug-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI-CTCAE v. 5.0 criteria, by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade per NCI CTCAE v. 5.0 criteria.	
PRO Analyses: A separate pre-specified PRO analysis following FDA and EMEA PRO Guidelines will be performed and detailed in a separate Statistical Analysis Plan (SAP) and PRO report. Scoring of PRO instruments and derivation of utility for health economic analysis will also be described in a separate analysis document.	
Interim Analyses: No interim analysis of efficacy is planned. Interim analyses for safety monitoring will occur when approximately 25%, 50%, and 75% of the planned total number of patients have been treated. A Data Monitoring Committee (DMC) will meet to assess the cumulative safety data and recommend study continuation, discontinuation, or study modification. A description of the roles and responsibilities of the DMC and details of the review processes are provided in a separate DMC charter.	

Table 1: Schedule of Events

Evaluations on Day 1 (D1) of a cycle should be performed within 24 hours prior to dosing, unless otherwise noted. Procedures already performed during the screening period within 72 hours prior to dosing do not need to be repeated on Cycle 1, Day 1 (C1D1). The End of Treatment (EOT) visit must be performed 0-7 days after the decision is made to discontinue study treatment (for patients who discontinue at a planned study visit, that visit may be considered the EOT visit if all assessments required at EOT are performed).

Please note: assessments for patients who enter the study extension phase following study completion (see protocol Section Section 3.4) are detailed in Table 1A.

	Screening (days prior to randomization)		**Randomization**	**Treatment Period (1 cycle = 21 days)**				**Safety Follow-up**		**Survival Follow-up Period**	**Notes**
				Cycle 1			**Cycles ≥2**	**End of Tx (+0-7 days)**	**30 (±3) days After Last Dose**		The first dose of study therapy should be administered within 72 hours after randomization. Notes that refer to timing with respect to dosing refer only to on-treatment assessments; post-discontinuation assessments may be performed at any time.
				Day			**Day**				
	28 days	**14 days**		**1**	**8 (±3d)**	**15 (±3d)**	**1 (±3d)**				
Written informed consent (pre-screening ICF)	See notes										To be obtained prior to any pre-screening evaluations.
Assessment of *FGFR2* gene rearrangement status (Pre-Screening)	See notes										Testing by designated central laboratory at any time prior to signing of main ICF.
Written informed consent (main ICF)	X										May be obtained at any time after confirmation of *FGFR2* gene rearrangement status and prior to randomization.
Demographics/medical history	X										
Pre-existing signs and symptoms	X			X							
Physical examination		X		X			X	X	X		Within 24 hours prior to dosing on D1 of each treatment cycle.
Vital signs		X		X			X	X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and weight		X		X			X	X	X		Height at screening only.

	Screening (days prior to randomization)		Randomization	Treatment Period (1 cycle = 21 days)				Safety Follow-up		Survival Follow-up Period	Notes
				Cycle 1			Cycles ≥2	End of Tx (+0-7 days)	30 (±3) days After Last Dose		The first dose of study therapy should be administered within 72 hours after randomization. Notes that refer to timing with respect to dosing refer only to on-treatment assessments; post-discontinuation assessments may be performed at any time.
				Day			Day				
	28 days	14 days		1	8 (±3d)	15 (±3d)	1 (±3d)				
Ophthalmological examination	X						(X)	X	X		At screening and 4-6 weeks after first dose; additional on-study evaluation as needed due to local requirements, physician judgment, and/or symptoms or signs of mineral deposits.
ECOG performance status		X		X			X	X	X		Within 24 hours prior to dosing on D1 of each cycle.
12-Lead electrocardiogram		X		X			X	X	X		ECG on C2D1 performed prior to collection of PK samples for that day.
Hematology and coagulation		X		X	X	X	X	X	X		Within 24 hours prior to treatment on D1 of each cycle, prior to treatment on C1D8 and C1D15, and as clinically indicated.
Chemistry (serum or plasma)		X		X	X	X	X	X	X		Within 24 hours prior to treatment on D1 of each cycle, prior to treatment on C1D8 and C1D15, and as clinically indicated.
Pregnancy test	See notes.			X			X	X	X		Serum pregnancy test required for WOCBP at screening (within 7 days prior to randomization) and end of treatment; serum or urine pregnancy test required at all other timepoints.
Blood PK sampling (required for patients receiving futibatinib only)							X				Blood samples (1 mL) collected C2D1 pre-dose (from -30 min to just before dose) and at 1h and 3h (±30 min) post-dose.
ctDNA blood samples		X						X			Minimum of 20 mL whole blood at screening and EOT. Patients who cross-over from the Control to the Experimental arm should provide an additional sample at the EOT for futibatinib.

	Screening (days prior to randomization)		Randomization	Treatment Period (1 cycle = 21 days)				Safety Follow-up		Survival Follow-up Period	Notes
				Cycle 1			Cycles ≥2	End of Tx (+0-7 days)	30 (±3) days After Last Dose		The first dose of study therapy should be administered within 72 hours after randomization. Notes that refer to timing with respect to dosing refer only to on-treatment assessments; post-discontinuation assessments may be performed at any time.
				Day			Day				
	28 days	14 days		1	8 (±3d)	15 (±3d)	1 (±3d)				
Blood for CA19-9		X					X	X			Samples collected at the same time as samples for clinical laboratory assessments at the end of every 2 cycles up to C4, and every 3 cycles thereafter (or as clinically indicated).
Prior & concomitant medications, AE assessments	X →							X	X		Collect from the time main informed consent is signed through 30 days after administration of the last dose of study therapy or until the start of new anticancer therapy, whichever is earlier. AEs directly associated with a pre-screening procedure should be reported as described in the study protocol.
PRO (EORTC QLQ-BIL21, EORTC QLQ-C30)		X					X	X			Evaluated at screening and as close as possible to the tumor assessment schedule: at the end of every 2 cycles (± 7 days) through Cycle 4 and every 3 cycles (±7 days) thereafter until disease progression or initiation of new anticancer therapy (whichever is first).
Baseline tumor assessments / scans	X										Baseline tumor assessments/scans must be obtained within **28 days** prior to randomization.

	Screening (days prior to randomization)		Randomization	Treatment Period (1 cycle = 21 days)				Safety Follow-up		Survival Follow-up Period	Notes
				Cycle 1			Cycles ≥2	End of Tx (+0-7 days)	30 (±3) days After Last Dose		The first dose of study therapy should be administered within 72 hours after randomization. Notes that refer to timing with respect to dosing refer only to on-treatment assessments; post-discontinuation assessments may be performed at any time.
				Day			Day				
	28 days	14 days		1	8 (±3d)	15 (±3d)	1 (±3d)				
Tumor assessments / scans							X	X		(X)	Tumor assessments/scans at the end of every 2 cycles (± 7 days) up to Cycle 4. Thereafter, tumor assessments may be performed every 3 cycles (± 7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever occurs first). At EOT, tumor assessment must be performed if the prior scan was performed ≥9 weeks prior to discontinuation of treatment if the patient discontinued for reasons other than radiologic disease progression. After EOT, patients who discontinued for reasons other than radiologic disease progression should continue to receive tumor assessments every 3 cycles (± 7 days), or as clinically indicated, until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).

	Screening (days prior to randomization)		Randomization	Treatment Period (1 cycle = 21 days)				Safety Follow-up		Survival Follow-up Period	Notes
				Cycle 1			Cycles ≥2				The first dose of study therapy should be administered within 72 hours after randomization. Notes that refer to timing with respect to dosing refer only to on-treatment assessments; post-discontinuation assessments may be performed at any time.
				Day			Day	End of Tx (+0-7 days)	30 (±3) days After Last Dose		
	28 days	14 days		1	8 (±3d)	15 (±3d)	1 (±3d)				
Survival status										X	After discontinuation of treatment, survival follow-up should occur every 3 months (±2 weeks) for up to 18 months after the randomization of the last patient.
Administer futibatinib				X							Continuous dosing (patients randomized to or crossing over to futibatinib only)
Administer gemcitabine / cisplatin				X	X		X				On Days 1 and 8 of each Cycle, up to a maximum of 8 cycles (patients randomized to gemcitabine / cisplatin only).

Table 1A: Schedule of Events – Study Extension Phase

	Treatment Period (1 cycle = 21 days)		Safety Follow-up	Notes
	Daily	At Least Every 3 Cycles	30 (±3) Days After last Dose	
Physical examination		X	X	Within 24 hours prior to dosing on D1 of each treatment cycle.
Vital signs		X	X	Heart rate, blood pressure, body temperature, and respiration rate.
Weight		X	X	
Ophthalmological examination		(X)	X	As needed due to local requirements, physician judgment, and/or symptoms or signs of mineral deposits.
ECOG performance status		X	X	Within 24 hours prior to dosing on D1 of each cycle.
12-Lead electrocardiogram		X	X	
Hematology and coagulation		X	X	Within 24 hours prior to treatment on D1 of each cycle and as clinically indicated.
Chemistry (serum or plasma)		X	X	Within 24 hours prior to treatment on D1 of each cycle
Pregnancy test		X	X	Serum or urine pregnancy test required at all timepoints.
Prior & concomitant medications, AE assessments		X	X	Collect from the time main informed consent is signed through 30 days after administration of the last dose of study therapy or until the start of new anticancer therapy, whichever is earlier.
Tumor assessments / scans		X		Tumor assessments may be performed as necessary to determine continued benefit from treatment, every 3 cycles (± 7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever occurs first).
Administer futibatinib	X			Continuous dosing

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
CCA	cholangiocarcinoma
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	Cytochrome P450
DCR	disease control rate
DMC	Data Monitoring Committee
DOR	duration of response
eCCA	extrahepatic cholangiocarcinoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
I.V.	intravenous
iCCA	intrahepatic cholangiocarcinoma
ICF	informed consent form
ICH	International Conference on Harmonisation
ICR	independent central review
IEC	independent ethics committee
IRB	institutional review board
IXRS	Interactive Voice/Web Response System
KM	Kaplan-Meier
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival

PD	progressive disease
PFS	progression-free survival
PFS2	PFS on next-line therapy
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetic(s)
Pop PK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PS	performance status
QD	daily
QTcF	Fridericia's corrected QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TID	three times per day
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman/women of child-bearing potential

1. INTRODUCTION

1.1. Disease Background

Cholangiocarcinoma (CCA), a bile duct cancer, is a rare tumor that arises from the malignant transformation of epithelial cells of the bile ducts. It is typically classified as either intrahepatic (iCCA) or extrahepatic (eCCA). Intrahepatic cholangiocarcinoma develops in the smaller bile ducts inside the liver and is the least common form of the disease (approximately 10%), whereas eCCA includes cancers in the peri-hilar (also known as Klatskin tumour) and distal bile duct area and is most common (approximately 90%) (Khan et al. 2002).

For disease that is localized at diagnosis, surgical resection offers the only chance of cure in patients with CCA. Unfortunately, symptoms are not usually apparent until CCA is at an advanced stage; thus, most patients (>65%) have disease which is unresectable at diagnosis.

The prognosis of patients with Stage III or IV CCA is extremely poor, with 5-year survival rates of 10% and 0%, respectively (Lamarca et al. 2014), and a median overall survival (OS) of 8 to 12 months (Goral 2017). Since the majority of patients are diagnosed after the opportunity for surgical resection has passed, this translates to very high mortality among affected patients. The life-threatening nature of the malignancy is compounded by a gradually rising incidence (Goral 2017) and mortality (Khan et al. 2008), especially among patients with iCCA.

Although there are no approved treatments in this setting, gemcitabine/cisplatin is the current standard first-line chemotherapy regimen for patients with advanced, metastatic, unresectable CCA. This was based on a randomized study comparing cisplatin plus gemcitabine with gemcitabine alone in randomized 410 patients with biliary tract cancer where median progression-free survival (mPFS) was 8.0 months in the cisplatin–gemcitabine group and 5.0 months in the gemcitabine-only group (Valle et al. 2010). In other prospective studies published between 2004 and 2013 in patients with advanced biliary tract cancers, treatment with gemcitabine/cisplatin resulted in mPFS ranging from 4.0 to 8.0 months and median OS ranging from 4.6 to 11.7 months (Park et al. 2015).

1.2. Futibatinib (TAS-120)

1.2.1. Background and Nonclinical Overview

The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling axis has been well characterized for its role in proliferation, differentiation, migration, and survival of cells, and it is fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults. Accordingly, dysregulation of this signaling pathway has been associated with many developmental disorders and cancer.

Futibatinib is a novel and selective small molecule FGFR inhibitor, which is the first irreversible, covalent inhibitor of FGFR1–4 being tested in humans. Futibatinib selectively and irreversibly binds to FGFR to exert an inhibitory effect on the FGF/FGFR pathway. Preclinical studies have shown that futibatinib selectively inhibits the cell growth of human cancer cell lines bearing FGFR gene abnormalities; strong antitumor efficacy has been observed with futibatinib in nude mouse or nude rat xenograft models bearing tumors with FGFR gene abnormalities.

Of note, aberrations in FGF or the FGFR are a reported genetic modification in CCA (Ang 2015). In iCCA, *FGFR2* gene rearrangements (including gene fusions) have been identified as an early driver of oncogenic events; these gene rearrangements are present in an estimated 10% to 20% of patients (Ang 2015; Arai et al. 2014; Borad et al. 2015; Goyal et al. 2017). Therefore, inhibiting the FGFR pathway in patients with CCA is a plausible therapeutic strategy for appropriately selected patients with this disease.

1.2.2. Clinical Overview

On the basis of encouraging *in vitro* and *in vivo* data, briefly excerpted above and outlined in full in the Investigator's Brochure, a clinical development program was initiated for futibatinib. To date, 2 clinical studies in healthy volunteers have been completed: 1 bioequivalence study assessing 2 dosage forms, and 1 food effect study. Two studies assessing the safety, efficacy, and pharmacokinetics (PK) of futibatinib in advanced cancers are currently ongoing: Study 10059010, a Phase 1 trial in Japanese patients with advanced solid tumors, and Study TAS-120-101, a Phase 1/2 trial in three parts:

- A Phase 1 Dose Escalation portion (completed with a total of 86 patients receiving either daily or 3-times-per-week dosing);
- A Phase 1 Dose Expansion portion, which includes additional cohorts in CCA, gliomas, urothelial carcinoma, and basket cohorts with *FGF/FGFR* aberrations; and
- A Phase 2 study initiated in April 2018, evaluating futibatinib at a daily (QD) dose of 20 mg, in patients with iCCA harboring *FGFR2* gene rearrangements.

The Phase 2 portion of this study was initiated based on strong evidence of antitumor activity in CCA in the Phase 1 part of the study. As of 01 January 2019, 54 patients with iCCA harboring *FGFR2* rearrangements were treated at 16 mg and 20 mg QD and followed for at least 6 months. The objective response rate (ORR) assessed by independent central review (ICR) was 25.9%, and the overall disease control rate (DCR) was 74.1% (95% confidence interval [CI]: 60.4, 85.0). Median duration of treatment was 6.1 months. Nine of the 54 patients were ongoing as of data cut-off.

Collectively, safety data from clinical trials suggest that futibatinib is tolerable in patients with advanced cancers. The most frequently reported treatment-related adverse event (AE) overall has been hyperphosphatemia (approximately 87%), mostly of Grades 1-2 (approximately 15% were Grade 3) and without clinical complications. Other frequently reported treatment-related AEs included the gastrointestinal system disorders of diarrhea, dry mouth, nausea, and stomatitis. Dry skin and increased liver enzymes were also reported, most of which were mild to moderate in severity.

Safety concerns that have been identified from preclinical studies of futibatinib include an increase of inorganic phosphorus in plasma, ectopic mineralization in various organs and tissues, lesions in bone/cartilage, and corneal lesions. An embryo-fetal developmental toxicity study conducted in rats showed that futibatinib inhibited normal development of the rat embryo-fetus and resulted in embryo-fetal lethality. Effective contraception is mandated for any patients receiving futibatinib who are of child-bearing potential and their partners.

1.3. Summary of Study Rationale

Aberrations in FGF or the FGFR are a reported genetic modification in CCA. In iCCA, *FGFR2* gene rearrangements, including gene fusions, have been identified as an early driver of oncogenic events. Futibatinib, a selective small molecule FGFR inhibitor, has shown promising antitumor activity in preclinical studies and ongoing clinical studies against a variety of tumor types harboring *FGFR* aberrations.

The Phase 3 study described in this protocol will evaluate the safety and efficacy of futibatinib against that of the current standard of care (gemcitabine-cisplatin chemotherapy) in the first-line treatment of patients with advanced CCA harboring *FGFR2* gene rearrangements (including gene fusions).

The maximum tolerated dose of futibatinib is 20 mg QD (continuous daily dosing), based on the results of the Phase 1 dose escalation portion of Study TAS-120-101. Accordingly, the starting dose of futibatinib in this Phase 3 study is 20 mg QD.

2. OBJECTIVES AND ENDPOINTS

The objective of this study is to compare the following endpoints (Table 2) in patients with advanced iCCA harboring *FGFR2* gene rearrangements, who are treated with either futibatinib monotherapy or gemcitabine-cisplatin chemotherapy.

Table 2: Objectives and Endpoints

Primary	
• PFS by ICR, based on Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1)	**PFS per central assessment,** defined as the time from date of randomization to the date of documentation of disease progression by ICR, or date of death, whichever occurs first.
Secondary	
• ORR	**ORR:** defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR) (per RECIST 1.1), based on ICR.
• DCR	**DCR,** defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR (per RECIST 1.1), based on central assessment of radiologic images.
• OS	**OS,** measured from the date of randomization until the date of death due to any cause.
• PFS according to Investigator assessment of radiologic images based on RECIST 1.1	**PFS per Investigator assessment,** defined as the time from date of randomization to the date of disease progression based on Investigator assessment of radiographic images or death, whichever occurs first.
• Safety and tolerability	Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), clinical laboratory tests, vital signs, ophthalmological exams, and 12-lead electrocardiogram (ECG).
Exploratory	
• Duration of response (DOR).	**DOR,** defined as the time from the first documentation of response (per RECIST 1.1 and based on ICR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first.
• Patient-reported outcomes (PRO)	**PRO** measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-BIL21 and QLQ-C30.
• PFS on next-line therapy (PFS2)	**PFS2,** defined as the time from randomization to subsequent disease progression per ICR after initiation of next-line therapy or death from any cause (whichever occurs first).
• Population pharmacokinetics (Pop PK) of futibatinib.	Blood samples for Pop PK analysis will be obtained from all patients receiving futibatinib on Cycle 2, Day 1, pre-dose and at 1 hour and 3 hours (±30 min) post-dose.

3. INVESTIGATIONAL PLAN

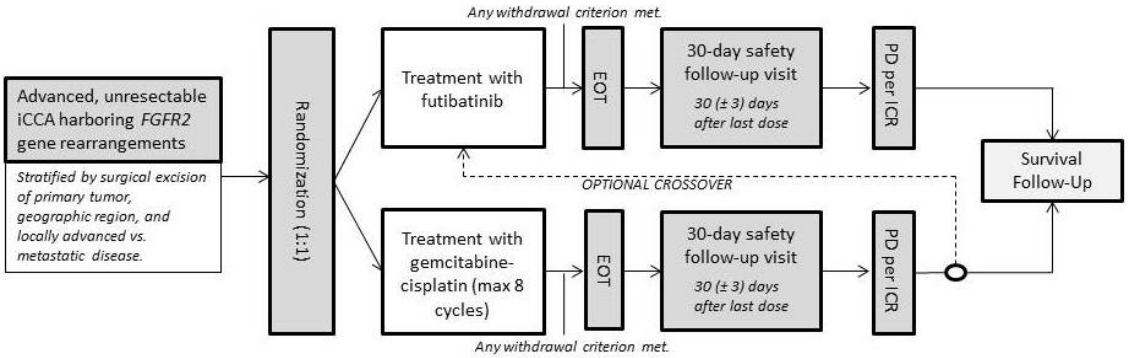
3.1. Overview of Study Design

Study TAS-120-301 (Figure 1) is an open-label, multinational, parallel 2-arm, randomized Phase 3 study evaluating the efficacy and safety of futibatinib versus gemcitabine-cisplatin chemotherapy as first-line treatment of patients with advanced, metastatic, or recurrent unresectable iCCA harboring *FGFR2* gene rearrangements. Eligible patients will be randomized on a 1:1 basis to the following study arms:

- **Experimental Arm:** Patients will receive futibatinib at an oral dose of 20 mg, administered QD on every day of a 21-day cycle.
- **Control Arm:** On Days 1 and 8 of a 21-day cycle, patients will receive:
  - Cisplatin 25 mg/m^2 in 1000 mL 0.9% saline by intravenous (I.V.) infusion over 1 hour, followed by 500 mL 0.9% saline over 30 minutes; and
  - Gemcitabine 1000 mg/m^2 in 250-500 mL 0.9% saline by I.V. infusion over 30 minutes, beginning after completion of the cisplatin and saline infusions.

Patients in the Experimental Arm may continue to receive continuous futibatinib until documentation of progressive disease (PD) per RECIST 1.1, or until other withdrawal criteria are met, whichever comes first. However, treatment may continue following PD per RECIST 1.1 if the patient is clinically stable and is considered by the Investigator to be deriving continued clinical benefit from futibatinib.

Patients in the Control Arm may receive gemcitabine-cisplatin chemotherapy for up to 8 cycles or until PD or other withdrawal criteria are met, whichever comes first. Patients who discontinue gemcitabine-cisplatin due to documented disease progression (by ICR) may receive treatment with futibatinib ("crossover"), if medically appropriate in the opinion of the Investigator and if criteria for futibatinib treatment are met. Patients who discontinue gemcitabine-cisplatin for other reasons (eg, safety, withdrawal of consent, Investigator decision) are eligible for crossover following subsequent ICR-confirmed PD.



Abbreviations: EOT=end of treatment; FGFR2=fibroblast growth factor receptor 2; iCCA=intrahepatic cholangiocarcinoma; ICR=independent central review; PD=progressive disease.

Figure 1: Study Schema

3.2. Scientific Rationale for Study Design

Please see Section 1.3.

3.3. Study Period

3.3.1. Study Periods and Visits for Each Patient

The study periods / visits described in this section are defined for all patients; please see Table 1 (Schedule of Events) for an outline of all assessments to be performed during each study period / visit. Please note:

- For all patients, the Safety Assessment Period begins at the time the informed consent form (ICF) is signed for the study (that is, the beginning of the Screening Period) and continues until at least 30 days after the last day of study therapy (that is, the end of the Safety Follow-up Period). After the 30-day Safety Follow-Up Visit (see below), patients will be assessed for drug-related SAEs only.
- For each patient, the Study Duration is defined as the time from day of ICF signature to the last day of Disease Assessment Follow-up / Survival Follow-up (see below).

3.3.1.1. Pre-Screening

Determination of *FGFR2* gene rearrangement status per the methods described in Section 6.1 of this protocol is required in order to assess eligibility for this study. This determination is considered a pre-screening assessment, and should be performed prior to all other screening / baseline evaluations. A pre-screening ICF, separate and distinct from the main study ICF, must be signed before any pre-screening evaluations may be performed.

3.3.1.2. Screening Period

The Screening Period is defined as the time from the time the patient completes the main study ICF until the date and time of first dose of study therapy. Determination of eligibility is based on the entry criteria enumerated in Section 4.1 and Section 4.2. No protocol-specific procedures or assessments may be performed prior to completion of the ICF, except for pre-screening (see above) or procedures that represent standard-of-care.

3.3.1.3. Patient Enrollment

Once the ICF is signed, the patient will be assigned a unique patient identification number. Once study eligibility is confirmed, the patient will be randomized into the appropriate treatment cohort (see Section 3.5). The patient should receive the first dose of study therapy within 3 days following randomization.

3.3.1.4. Treatment Period and End of Treatment Visit

Treatment discontinuation may occur for any of the reasons listed in Section 4.5. The treatment period is the time from the date of first dose of study therapy (Day 1) to the date of last dose of study therapy. An end-of-treatment (EOT) visit must be performed within 7 days after the decision is made to discontinue study treatment; at this visit, every effort should be made to perform the assessments outlined in Table 1. For patients who discontinue at a planned study

visit, that visit may be considered the EOT visit if all assessments required at EOT are performed.

3.3.1.5. Safety Follow-Up Period and 30-Day Safety Follow-Up Visit

The safety follow-up period is the time from the date of last dose of study therapy through the 30-day safety follow-up visit, which must be performed 30 days (±3 days) following the last dose of study therapy. If the patient starts new anticancer therapy within 30 days of the last dose of study therapy, the 30-day safety follow-up visit should be performed before the start of new anticancer therapy. Every effort should be made to perform the assessments outlined in Table 1. If the patient is unable to return to the study site, a follow-up phone call can be made by the study site to collect any new safety information that occurred during the Safety Follow-up Period.

After the 30-day Safety Visit, only AEs that are serious and drug-related will be assessed.

3.3.1.6. Post-Discontinuation Considerations

3.3.1.6.1. Crossover

Patients randomized to the Control Arm who experience documented PD per RECIST 1.1 (by ICR) are eligible to crossover to receive futibatinib 20 mg QD. Patients who discontinue gemcitabine-cisplatin for other reasons are not eligible to crossover until there is documentation of ICR-confirmed radiographic disease progression. Crossover is optional and is at the discretion of the Investigator. Patients who crossover should receive their first dose of futibatinib in the crossover period within 30 days after documentation of PD by ICR or within 30 days after completion of the 30-day safety follow-up period, whichever is later.

Please note that for patients who crossover, the 30-day safety follow-up period must be completed prior to the first dose of futibatinib in the crossover period. A new tumor scan must be performed as a new baseline if the most recent scan was performed >6 weeks prior to the first dose of futibatinib in the crossover period.

In addition to the above considerations, patients must meet all of the criteria in Section 4.3 in order to be eligible for crossover.

3.3.1.6.2. Discontinuations for Reasons Other than Disease Progression

Patients who discontinue without documented disease progression per RECIST 1.1 should continue to undergo tumor assessments/scans according to the Schedule of Events (that is, every 6 weeks or 9 weeks ±7 days until PD is documented, new anticancer therapy is initiated, the study is terminated, or the patient dies, withdraws consent, or is lost to follow-up).

3.3.1.6.3. Survival Follow-Up

Once disease progression per RECIST 1.1 is confirmed or the first subsequent new anticancer therapy is initiated, whichever occurs first, the survival follow-up period begins. During this period, the patient or family should be contacted for survival follow-up every 12 weeks (±2 weeks) until withdrawal of consent, death, or loss to follow up, until study completion as defined in Section 3.4. In addition, all subsequent anticancer treatments will be recorded.

3.4. Study Completion and Study Extension

The study will be considered complete:

- 12 months after the last event has been observed for the primary analysis of efficacy (that is, 12 months after 162 PFS events are reported); or
- The trial is halted early for any reason.

Following Study Completion, patients still receiving and deriving benefit from study therapy in the opinion of the Investigator following discussion with the Sponsor will be permitted to continue treatment in a Study Extension phase. During the Study Extension, patients may receive treatment until withdrawal criteria are met.

During this period, all safety assessments are to continue according to the schedule in Table 1A. However, electronic data collection will be reduced. Specifically, study extension data collection is to include, at a minimum:

- Study drug administration;
- Study drug accountability;
- Serious adverse events;
- Non-serious adverse events that are related to study treatment or result in treatment discontinuation; and
- Any cases of pregnancy, overdose, or medication error.

3.5. Randomization and Blinding

3.5.1. Randomization

This is a randomized study. The eligibility of all patients must be verified prior to enrollment. Study sites will enter patient demographic and baseline data into the electronic data capture (EDC) system in order to obtain a subject number.

Once patient confirmation of eligibility and the criteria for randomization have been met, Investigators will enroll patients. Patients will be centrally randomized in a 1:1 ratio to futibatinib or gemcitabine-cisplatin via an Interactive Voice/Web Response System (IXRS).

Patients will be stratified by the following balancing factors:

- Prior surgical excision of the primary tumor (yes vs. no);
- Geographic region (Asia vs. rest of the world); and
- Locally advanced vs. metastatic disease.

The IXRS will assign kit numbers corresponding to the patient's administration assignment, inform the study site user of the kit number that has been assigned to the patient, and provide instructions for the dispensing of the study drug.

No patients will be replaced at any time during this study.

3.5.2. Blinding

Futibatinib is administered orally, while the comparator treatment (gemcitabine-cisplatin) is administered by I.V. infusion. Accordingly, this is an open-label (non-blinded) study.

3.6. Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of the patients enrolled in this study. The committee will meet to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. The details will be provided in a separate DMC charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Determination of *FGFR2* gene rearrangement status should be completed before the patient undergoes any protocol-specific procedures. Waivers will not be granted for any of the eligibility criteria.

4.1. Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for this study.

1. Provide written informed consent.
2. Is ≥ 18 years of age (or meets the country's regulatory definition for legal adult age).
3. The patient has histologically confirmed, locally advanced, or metastatic, or recurrent unresectable iCCA harboring *FGFR2* gene rearrangements based on testing performed by the designated central laboratory.
4. Patient has radiographically measurable disease per RECIST 1.1.
5. Patients who have received treatment for locally advanced disease (for example, trans-arterial chemoembolization, selective internal radiation therapy, external beam radiation) must have evidence of radiographic progression with measurable disease outside the previously-treated lesions.
6. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.
7. Adequate organ function as defined by the following criteria:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5 × ULN.
   - Total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN for patients with Gilbert's syndrome.
   - White blood cell (WBC) count ≥ 2000/mm^3 (≥ 2.0 × 10^9/L)
   - Absolute neutrophil count (ANC) ≥ 1000/mm^3 (ie, ≥ 1.0 × 10^9/L)
   - Platelet count ≥ 100,000/mm^3 (≥ 100 × 10^9/L)
   - Hemoglobin ≥ 9.0 g/dL
   - Phosphorus ≤ 1.5 × ULN
   - Creatinine clearance ≥ 60 mL/min
8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test within 7 days prior to administration of the first dose of futibatinib. Female patients are not considered to be of child-bearing potential if they have a history of hysterectomy or are post-menopausal defined as no menses for 12 months without an alternative medical cause. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 3 months after the last dose.
9. Willing and able to comply with scheduled visits and study procedures.

4.2. Exclusion Criteria

A patient must not meet any of the following exclusion criteria to be eligible for participation in this study:

1. Patient has received previous systemic anticancer therapy
    - Patients receiving adjuvant or neoadjuvant treatment and completed ≥6 months prior to randomization are eligible
2. Patient has mixed hepatocellular carcinoma – iCCA disease.
3. History and/or current evidence of any of the following disorders:
    - Non-tumor related alteration of calcium-phosphorus homeostasis that is clinically significant in the opinion of the Investigator.
    - Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator.
    - Retinal disorder confirmed by retinal examination and considered clinically significant in the opinion of the ophthalmologist.
4. History or current evidence of uncontrolled ventricular arrhythmias
5. Fridericia's corrected QT interval (QTcF) > 470 ms on ECG conducted during Screening.
6. Treatment with any of the following within the specified time frame prior to the first dose of study therapy, or failure to recover from side effects of these prior therapies:
    - Major surgery within the previous 4 weeks (the surgical incision should be fully healed prior to the first dose of study therapy).
    - Radiotherapy (any dose) for extended field within 4 weeks or limited field radiotherapy within 2 weeks, and/or has not recovered from acute impact of radiotherapy.
    - Patients with locoregional therapy, e.g. transarterial chemoembolization, selective internal radiotherapy, or ablation within 4 weeks.
    - Any history of liver transplant.
7. A serious illness or medical condition(s) including, but not limited to, the following:
    - Brain metastases that are untreated or clinically or radiologically unstable (that is, have been stable for <1 month).
    - Known acute systemic infection.
    - Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months.
    - Chronic nausea, vomiting, or diarrhea considered to be clinically significant in the opinion of the Investigator.

- Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the judgment of the Investigator would make the patient inappropriate for entry into this study.

8. Patients with a history of another primary malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen in the opinion of the Investigator.
9. Pregnant or breast-feeding female
10. The patient is unable to take oral medication.

4.3. Entry Criteria for Crossover

In addition to the considerations outlined in Section 3.3.1.6.1, patients must meet all of the following criteria to be eligible for crossover:

- Any gemcitabine-cisplatin-induced toxicity has resolved to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade ≤1;
- ECOG PS 0-1
- Adequate organ function as defined by:
  - AST and ALT ≤ 3 × the ULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5 × ULN;
  - Total bilirubin ≤ 1.5 × ULN, or ≤ 3 × ULN for patients with Gilbert's syndrome.
  - ANC ≥ 1000/mm^3 (≥ 1.0 × 10^9/L)
  - Platelet count ≥ 75,000/mm^3 (≥ 75 × 10^9/L by IU)
  - Hemoglobin ≥ 9.0 g/dL
  - Phosphorus ≤ 1.5 × ULN
  - Creatinine clearance: ≥ 40 mL/min.
- Does not meet any of the following exclusion criteria:
  - Current evidence of any of the following disorders:
    - Non-tumor related alteration of calcium-phosphorus homeostasis that is clinically significant in the opinion of the Investigator.
    - Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator.
    - Retinal disorder confirmed by retinal examination and considered clinically significant in the opinion of the ophthalmologist.
  - Current evidence of uncontrolled ventricular arrhythmias
  - QTcF > 470 ms on ECG.
  - A serious illness or medical condition(s) including, but not limited to, the following:

- Brain metastases that are untreated or clinically or radiologically unstable (that is, have been stable for <1 month).
- Known acute systemic infection.
- Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months.
- Chronic nausea, vomiting, or diarrhea considered to be clinically significant in the opinion of the Investigator.
- Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the judgment of the Investigator would make the patient inappropriate for entry into this study.

o Pregnant or breast-feeding female.

4.4. Screen Failure

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE occurring after completion of the ICF.

Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened a maximum of 3 times. Rescreened patients should be assigned the same subject identification code as for the initial screening.

4.5. Discontinuation of Treatment

If a patient meets any of the following conditions during the clinical study period, study treatment may be discontinued.

- Radiographic PD based on RECIST 1.1 as determined by ICR;
- Clinical or radiographic PD per Investigator assessment;
- Unacceptable AEs, or change in underlying condition such that the patient can no longer tolerate therapy, as evidenced by a dose delay > 21 days from the scheduled start date of the next cycle or need for more than the allowable number of dose reductions outlined in this protocol;
- Physician's decision, including need for other anticancer therapy not specified in the protocol, or surgery or radiotherapy to the only site(s) of disease being followed in the study;
- Pregnancy;
- A significant protocol deviation which, in the opinion of the Investigator and/or Sponsor, renders the patient unsuitable for further study treatment;
- Loss to follow-up;

- Death;
- Termination of the study by the Sponsor; or
- At the patient's request at any time irrespective of the reason.

Please note: patients who discontinue treatment for any reason other than radiographic PD per ICR (including clinical PD or radiographic PD per Investigator) should continue to undergo tumor assessments according to the schedule outlined in Table 1 until ICR-determined disease progression (unless the patient withdraws consent for these assessments or continued assessments are medically unfeasible in the opinion of the Investigator).

Patients who withdraw consent for further treatment may choose to remain on study (tumor assessments, survival follow-up, etc); in such a case, all study evaluations should continue as outlined in this protocol. If the patient withdraws consent to all follow-up assessments, the patient should be considered to have discontinued the study as described in Section 4.6.

4.6. Withdrawal from the Study

A patient may be discontinued from all study interventions and assessments (that is, discontinued from the study without follow-up) for any of the following reasons:

1. Death;
2. Loss to follow-up / contact despite best effort of investigative site personnel (that is, after at least 2 documented attempts to contact the patient and/or family); or
3. Patient withdrawal of consent to further follow-up assessments, irrespective of the reason.

5. STUDY TREATMENT

5.1. Study Drug Administration

A treatment cycle is defined as 21 days for both arms. However, patients in the Experimental Arm (or patients in the Control Arm who crossover to futibatinib treatment following PD per RECIST 1.1) receive continuous QD futibatinib with no planned interruption between cycles.

5.1.1. Futibatinib

Futibatinib is supplied as 4-mg tablets and will be taken orally (PO) at a dose of 20 mg QD.

Futibatinib should be administered under fasting conditions. It should be taken with a glass of water, on an empty stomach, every 24 hours in the morning or evening at the same time each day, if possible. No food should be consumed for 2 hours prior and 1 hour after the dose of futibatinib, but patients will be permitted to drink water during this period.

When a PK sample is collected on Cycle 2, Day 1 futibatinib should be administered on site after collection of the first PK sample.

In the event of a dosing delay up to 12 hours after the scheduled dosing time, the patient should still take that day's dose. If the dosing delay continues for >12 hours after the scheduled dosing time, or if the patient vomits after a dose, the patient should skip dosing for that day and not make up for it the following day.

5.1.2. Gemcitabine / Cisplatin

Gemcitabine and cisplatin will be administered to patients in the Control Arm on Days 1 and 8 of each 21-day cycle for up to 8 cycles.

The hydration and electrolyte regimen (KCl +/- $MgSO_4$) for cisplatin administration will be determined by locally agreed pharmacy procedures and guidelines. Anti-emetic premedication according to local guidelines is permitted.

Cisplatin will be administered at a dose of 25 mg/m^2 (in 1000 mL 0.9% saline) by I.V. infusion over 1 hour, followed by infusion of 500 mL 0.9% saline over approximately 30 minutes. After completion of the cisplatin and saline infusions, gemcitabine will be administered at a dose of 1000 mg/m^2 (in 250-500 mL 0.9% saline) by I.V. infusion over approximately 30 minutes.

5.1.3. Treatment Duration

Patients in the Control Arm may receive gemcitabine-cisplatin chemotherapy for up to 8 cycles or until PD or other withdrawal criteria are met (see Section 4.5), whichever comes first.

Patients in the Experimental Arm (or patients in the Control Arm who crossover to futibatinib treatment following PD per RECIST 1.1) may continue to receive futibatinib until PD or other withdrawal criteria are met (see Section 4.5), whichever comes first.

5.2. Dose and Schedule Modifications

5.2.1. Dose and Schedule Modifications for Futibatinib

5.2.1.1. General Considerations

This section defines general dose modification guidelines for patients receiving futibatinib in the Experimental Arm (or patients in the Control Arm who crossover to futibatinib treatment following PD).

The starting dose of futibatinib is 20 mg QD for all patients. A maximum of 2 dose reductions are permitted, to reduced doses of 16 mg QD (first reduction) and 12 mg QD (second reduction).

If dose reduction fails to result in achieving minimal criteria to resume treatment, or if toxicities occur which would necessitate reduction of the dose of futibatinib below 12 mg QD, the patient should be discontinued from futibatinib.

Following a dose reduction, if a benefit/risk assessment favors an increase of futibatinib dose up to the initial starting dose (20 mg QD), an agreement with the Sponsor's Medical Monitor is required prior to the dose increase.

If toxicities requiring dose reduction(s) do not recover based on the criteria defined in Table 3 through Table 5 within 21 days after the last dose of futibatinib, the patient will be discontinued permanently from treatment (Section 4.5). If resumption criteria are met within 21 days of the last dose of futibatinib, the patient may resume futibatinib treatment at the appropriate dose level.

5.2.1.2. Futibatinib Dose Modifications for Nonhematologic Toxicities

Dosing modification guidelines for nonhematologic toxicities are provided in Table 3. Dose modification guidelines for hyperphosphatemia is provided in Table 4.

If there is any uncertainty about continuing therapy or resuming therapy in a patient with nonhematologic AEs, the case must be discussed with the Sponsor's Medical Monitor prior to continuing futibatinib.

Table 3: Futibatinib Dosing Modification for Related Nonhematologic Toxicities

Grade	Dose Interruption/Resumption	Dose Adjustment
Grade 1 or 2	Maintain treatment at the same dose level	None
Grade 3	Withhold treatment until return to baseline or Grade ≤1	Reduce by 1 dose level from the previous level, except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication which does not require a dose hold or reduction.
Grade 4	Discontinue treatment	Permanent discontinuation of futibatinib.
Grade 4 (lab abnormality AE)	Withhold treatment	Futibatinib will be permanently discontinued if assessed by the Investigator as life threatening. If it is in the best interest of the patient to continue treatment in the opinion of the Investigator and after discussion with the Sponsor, the patient can resume treatment at a reduced dose level once toxicity returns to baseline or Grade ≤1.

Abbreviations: AE=adverse event.

Recommendations for hyperphosphatemia management are provided in Table 4. These are suggested guidelines based on emerging data from studies evaluating FGFR inhibitors, and from the experience of Investigators participating in ongoing studies of futibatinib.

Table 4: Recommendations for Hyperphosphatemia Management

Serum Phosphorus Result (mg/dL and mmol/L)[a]	Grade[b]	Futibatinib Dose Interruption and Modification Recommended Phosphate Binder for Management of Hyperphosphatemia[c]
ULN < P <5.5 (mg/dL) ULN < P <1.78 (mmol/L)	Grade 1	• No interruption, consider phosphate binder once serum phosphorus level is > ULN. • Should serum phosphorus level rapidly increase within 1 week, consider early phosphate-lowering therapy, eg, Sevelamer tablets 800 mg three times per day [TID].
5.5 ≤ P ≤7.0 (mg/dL) 1.78 ≤ P ≤2.26 (mmol/L)	Grade 2	• No interruption, implement phosphate binder (monotherapy or in combination), • Start with Sevelamer monotherapy (range from 800 mg TID to 2400 mg TID). • Re-assess serum phosphate within 7 days, and plan to escalate Sevelamer or add treatment with acetazolamide 250 mg QD or TID and/or lanthanum carbonate (Fosrenol®) 1.0 g QD or TID, and further titration[d], if phosphate level continues to increase.
7.0 < P ≤10.0 (mg/dL) 2.26< P ≤3.23 (mmol/L)	Grade 3	• Dose reduce futibatinib to the next lower dose level and intensify phosphate lowering therapy • If the serum phosphorus level has resolved to ≤ Grade 2 within 14 days after dose reduction, continue futibatinib at the reduced dose level. • Re-assess serum phosphate within 7 days and at least once a week. If the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days, further reduce futibatinib from the last reduced dose level (or no lower than 12 mg QD). • If the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days of the second dose reduction of futibatinib (or no lower than 12 mg QD), interrupt dosing with futibatinib until it is resolved to ≤ Grade 2 before resuming futibatinib at the reduced dose prior to dose interruption.
P >10.0 (mg/dL) P >3.23 (mmol/L)	Grade 4	• Interrupt futibatinib until it's resolved to ≤ Grade 2, then resume futibatinib at the next lower dose level and intensify phosphate lowering therapy. • Re-assess serum phosphate within 7 days and at least once a week. If after 2 dose interruptions and 2 dose reductions the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days, permanently discontinue futibatinib.

Abbreviations: P=phosphorus; QD=once a day; TID=three times a day; ULN=upper limit of normal

a. mmol/L = mg/dL × 0.3229 (conversion factor).
b. This grading for the range of serum phosphorus levels will be used for the protocol.
c. Phosphate binders can be used as monotherapy or in combination. Please consult the drug package insert. Sevelamer should be preferably taken in the middle of meals, both tablets and powder, in order to improve gastrointestinal tolerance and compliance. If Sevelamer cannot be used, other phosphate binders or hyperphosphatemia treatment drugs can be used. Lanthanum carbonate should be taken instead just after meals – tablets of Fosrenol® are large, but may be cut if required. No dose adjustments are needed in patients with renal or hepatic impairment.
d. Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached.

5.2.1.3. Futibatinib Dose Modifications for Hematologic Toxicities

Criteria for dose interruption and resumption for hematologic toxicities are presented in Table 5.

Table 5: Futibatinib Dose Interruption and Modification Criteria for Related Hematologic Toxicities

Worst toxicity CTCAE Grade (value)	Recommended dose modification any time during a cycle of futibatinib
Anemia (Hgb)	
Grade 1 (Hgb < LLN - 10.0 g/dL)	Maintain dose level
Grade 2 (Hgb < 10 – 8.0 g/dL)	Maintain dose level
Grade 3 (Hgb < 8.0 - 6.5 g/dL)	Withhold dose until resolved to ≤ Grade 1 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Grade 4 (life threatening consequences; urgent intervention indicated)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Maintain dose level
Grade 4 (ANC < 500/mm^3)	Withhold dose until resolved to ≤ Grade 2 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Febrile neutropenia (ANC < 1000/mm^3, with single temperature ≥ 38.3°C or sustained [>1 hour] temperature of ≥ 38.0°C)	Withhold dose until resolved, then reduce 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level

Abbreviations: ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; Hgb=hemoglobin; LLN=lower limit of normal; PLT=platelets.

5.2.2. Dose and Schedule Modifications for Gemcitabine and Cisplatin

5.2.2.1. General Considerations

This section defines general dose modification guidelines for patients receiving gemcitabine and cisplatin in the Control Arm.

5.2.2.2. Gemcitabine and Cisplatin Dose Modifications for Non-Hematologic Toxicities

Renal Toxicity

Eligible patients must have baseline creatinine clearance ≥60 mL/min (measured within 72 hours prior to dosing on C1D1; please see Table 1). At all administration timepoints, the dose of cisplatin is dependent upon renal function (that is, creatinine clearance); please see Table 6 for specific guidelines.

If a sudden increase in creatinine occurs, haemolytic uraemic syndrome should be ruled out.

Table 6: Cisplatin Dose Modification Guidelines for Renal Toxicity

CrCl (mL/min)	Cisplatin Dose
>60 mL/min	100% of planned dose
51 – 60 mL/min	75% of planned dose
40 – 50 mL/min	50% of planned dose
<40 mL/min	Repeat CrCl assessment, insuring adequate hydration • If repeat assessment shows CrCl ≥40 mL/min, proceed with cisplatin administration according to the guidelines in this table. • If repeat assessment shows CrCl <40 mL/min, cisplatin must be omitted until recovery of renal function

Abbreviations: CrCl=creatinine clearance.

If the cisplatin dose is reduced or omitted at any timepopint due to reduced renal function, gemcitabine may be administered without modification as long as CrCl remains ≥ 30 mL/min. Reduction to the dose of gemcitabine may be warranted in cases where CrCl is <30 mL/min.

Other Non-Hematologic Toxicity

Dose modification guidelines for other non-hematologic toxicities are summarized in Table 7.

Table 7: Gemcitabine-Cisplatin Dose Modification Guidelines for Non-Hematologic Toxicity

Description of Toxicity	Recommended dose modification
No dose reduction / modification required	
Alopecia (any grade)	Maintain dose level
Fatigue / Asthenia (Grade ≤ 2)	Maintain dose level
Nausea / Vomiting (Grade ≤ 2)	Maintain dose level; note that this includes patients with reductions from Grade 3-4 following appropriate use of anti-emetics.
Edema (Grade ≤ 2)	Maintain dose level; give postural advice and consider administration of appropriate diuretics.
Consider dose modification	
Fatigue / Asthenia (Grade ≥ 3)	Reduce gemcitabine dose by 25%; if toxicity does not respond to dose reduction, discontinue both gemcitabine-cisplatin
Nausea / Vomiting (Grade ≥ 3)	Ensure optimal use of antiemetics (according to local policy) Delay until recovery to baseline, then: Omit cisplatin first. If no improvement reduce gemcitabine by 25%; if toxicity does not respond to anti-emetic treatment or dose reduction of both gemcitabine-cisplatin, discontinue both gemcitabine-cisplatin
Peripheral neuropathy (Grade 2)	Delay cisplatin until recovery to baseline, then continue at full dose. If no recovery, treat as for Grade ≥3. Continue with gemcitabine (full dose).
Peripheral neuropathy (Grade ≥ 3)	Omit cisplatin from further treatment. Continue with gemcitabine (full dose).
Edema (Grade ≥ 3)	Dipstick urine test for protein followed by full 24-hour urinary protein estimation if result ≥+ Delay until recovery to baseline (with use of appropriate diuretics). Then reduce gemcitabine by 25%; if toxicity does not respond to diuretic treatment or dose reduction, discontinue both gemcitabine-cisplatin.
Tinnitus (any grade)	No dose modification required if full recovery between cycles. Omit cisplatin if no recovery between cycles. Continue gemcitabine (full dose).
Pulmonary toxicity (Grade ≥ 2)	Discontinue gemcitabine-cisplatin treatment and initiate supportive therapy (high dose steroids) immediately.

5.2.2.3. Gemcitabine and Cisplatin Dose Modifications for Hematologic Toxicities

Gemcitabine should be dose-reduced if haematological toxicity occurs, according to Investigator judgement and based on the guidelines outlined in Table 8.

Table 8: Gemcitabine-Cisplatin Dose Modification Guidelines for Hematologic Toxicity

WBC ($x10^9$/L)		ANC ($x10^9$/L)		Platelets ($x1000/mm^3$)	Gemcitabine Dose	Cisplatin Dose
≥2	and	≥1	and	≥100	Full	Full
1 – 1.9	and/or	0.5 – 0.9	and/or	50 – 99	75% dose	Full
<1	and/or	<0.5	and/or	<50	Delay[a]	Delay[a]

Abbreviations: ANC=absolute neutrophil count; WBC=white blood cell(s).

a. If the delay lasts >3 weeks, the patient should be discontinued from treatment.

5.3. Treatment Compliance

Each patient will be instructed to comply with the dosage and dosing regimen of futibatinib. Gemcitabine and cisplatin will be administered to patients in the Control Arm only in the clinic under the supervision of clinic staff; all details of administration will be recorded in the electronic case report form (eCRF).

Compliance with all study medication administration should be documented in the patient's source documents.

5.4. Concomitant Medications and Therapies

The following therapies are permitted:

- Bisphosphonates;
- Denosumab; and/or
- Steroids for patients with brain metastases.

Local or regional palliative cryotherapy or radiation, such as for bone pain or palliative surgery (non-anti-neoplastic intent), are permitted (provided the target lesion is not a site of measurable disease and is not indicative of disease progression). Study therapy should be ceased a minimum of 2 days prior to administration of palliative treatment, and may be resumed 7 days after the procedure or when the patient has recovered from the side effects of the procedure.

The following medications/therapies may be given concomitantly under the following guidelines:

Hematologic Support: may be administered as medically indicated (that is, blood transfusions, granulocyte colony-stimulating factor, erythropoietin stimulating agents) according to the institutional site standards or American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015).

Management of Diarrhea: Prophylactic treatment for diarrhea is permitted during the study if clinically indicated according to the institutional or published guidelines (Benson et al. 2004).

Management of Nausea/Vomiting: Antiemetics may be administered as clinically indicated according to institutional standards or ASCO guidelines (Hesketh et al. 2017).

5.4.1. Prohibited Medications and Therapies

Patients are not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or antineoplastic endocrine therapy during the study treatment period. If extended field radiation therapy or palliative radiation to a focal site of measurable disease are deemed in the best interest of the patient following discussion between the Investigator and the Sponsor, the patient will be censored for the primary analysis of efficacy.

5.4.2. Drug Interactions

Drug interaction studies with futibatinib have not been conducted in humans. The following information is based on results from *in vitro* studies. Caution is advised if these drugs are given concomitantly (see Appendix C).

Cytochrome P450 (CYP) 3A inhibitors and inducers: CYP3A is involved in the metabolism of futibatinib. CYP3A inhibitors and inducers may alter the concentration and activity of futibatinib.

CYP3A substrates: Futibatinib is a potential time-dependent inhibitor of CYP3A. Futibatinib may increase the concentration and activity of CYP3A substrates.

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors: Futibatinib is a potential inhibitor of P-gp and BCRP. Futibatinib may alter the PK and activity of P-gp and BCRP substrates.

P-gp and BCRP substrates: Futibatinib is a substrate of P-gp and BCRP. P-gp and BCRP inhibitors may alter the concentration and activity of futibatinib.

No specific drug interaction studies have been conducted for gemcitabine (gemcitabine prescribing information [PI]). For cisplatin, plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy (cisplatin PI). Please see the respective labels for gemcitabine and cisplatin for additional discussion of potential drug interactions with these agents.

5.5. Effective Contraception During Study

Female patients considered not to be of child-bearing potential must have a history of being postmenopausal (no menses for 12 months without an alternative medical cause), or hysterectomy that is clearly documented in the patient's source documents.

For WOCBP, including female study participants and partners of male participants, effective contraception is required during the study and for 3 months after the last dose of study medication. Effective contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner with documentation of the success of the vasectomy
- Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients with partners who are WOCBP should use a combination of male condom with cap, diaphragm, or sponge with spermicide during the study and for 3 months after the last dose of study medication. Donation of sperm or ova is not allowed during the study and for 3 months following the last dose of study drug.

5.6. Study Drug Materials and Management

Futibatinib will be supplied by the Sponsor; gemcitabine and cisplatin will be supplied by the Sponsor or procured by investigative sites, depending on local operational and regulatory requirements. Detailed information, including requirements for accountability, and disposal of study drug will be provided in a separate Pharmacy Manual.

5.6.1. Description of Study Drug

A description of the futibatinib study drug and packaging information are provided in Table 9. Please refer to the respective product labels for descriptions of gemcitabine and cisplatin.

Table 9: Futibatinib Product Description and Packaging Information

Product Description and Dosage Form	Potency/ Strength	Appearance	Primary Packaging
Futibatinib Tablet	4 mg	Round, white, film-coated tablet	Aluminum/Aclar blister

5.6.2. Packaging and Labeling

Futibatinib tablets will be packaged and labeled according to local regulations. Additional clinical labeling will be added as necessary.

Gemcitabine and cisplatin will follow the packaging and labeling specified on the respective labels, and will receive additional clinical labeling as required by local regulations.

5.6.3. Accountability

The Investigator is responsible for ensuring that all futibatinib received at the site is inventoried and accounted for throughout the study. Futibatinib will be stored and disposed of according to the Sponsor's instructions. The dispensing of futibatinib to the patient and the return of futibatinib from the patient must be documented in the patient's source documents/the drug accountability form. Patients must be instructed to return all original containers, whether empty or containing study drug.

Gemcitabine and cisplatin will be stored according to the product label and disposed of according to the Sponsor's instructions.

At the conclusion of the study, all study drugs supplied by the Sponsor must be destroyed or returned to the designated depot, per the instructions provided in the Pharmacy Manual.

6. STUDY ASSESSMENTS

6.1. Study Assessments and Procedures

The Schedule of Events (Table 1) summarizes the frequency and timing of all applicable study assessments, including allowable windows for study visits and assessments / procedures. Written informed consent must be provided before any study-related procedures are performed.

The study schedule must be followed; however, in unavoidable circumstances (e.g., holidays, weekends, etc.) a window of ± 3 days is allowable for study procedures as long as the proper order of procedures and assessments is maintained. The ± 3-day window does not apply to assessments on Day 1 of Cycle 1.

6.1.1. Determination of *FGFR2* Gene Rearrangement Status (Pre-Screening)

Determination of eligibility is based in part on the determination of *FGFR2* gene rearrangement status based on testing by the designated central laboratory,

Determination of *FGFR2* gene rearrangement status should be performed prior to any other screening / baseline assessments. Any AEs directly associated with a pre-screening procedure should be reported as described in Section 9.1.2. There is no need to record AEs and SAEs that occur between signing the pre-screening ICF and main study ICF if the events are unrelated to the pre-screening procedures, unless reporting is mandatory by local regulations.

6.1.2. General Assessments

The following general assessments are performed as indicated in the Schedule of Events.

- **Demographics / medical history:** Includes sex, age, clinical diagnosis, date and method of diagnosis, prior cancer therapy, and relevant medical history (past and concurrent).
- **Review eligibility criteria:** Eligibility is assessed during the screening period and should be confirmed on Day 1 of Cycle 1, prior to first dose of study therapy.
- **Physical examination**
- **Vital signs:** Pulse rate, systolic and diastolic blood pressure, body temperature, and respiration rate. Any abnormal reading should be repeatedly immediately.
- **Height and body weight:** Height is collected for the purpose of body mass index calculations at baseline only.
- **ECOG performance status:** See Appendix A.
- **Pregnancy test:** Serum β-human chorionic gonadotrophin (human chorionic stimulating hormone) test required for WOCBP at screening and end of treatment; serum or urine test required at all other timepoints listed in the Schedule of Events.
- **Concomitant medication:** Including all medications / therapies administered from the time ICF is signed through 30 days after administration of the last dose of study therapy or until the start of new anticancer therapy.

- **12-Lead ECG**: Single, resting, semirecumbent 12-lead ECG will be performed locally. Data collection includes RR interval (heart rate), QT interval, QTcF interval and abnormal findings; the Investigator is responsible for interpreting and measuring ECG data.

6.1.3. Efficacy Assessments

On-site tumor assessments (including computed tomography [CT]/magnetic resonance imaging [MRI]) will be performed by the Investigator/local radiologist according to RECIST 1.1 guidelines (Eisenhauer et al. 2009). Results of these assessments, including response for target and non-target lesions and appearance of new lesions, will be the basis for the continuation or discontinuation of study therapy. Response definitions are provided in Section 8.1 .

If the Investigator determines that a patient has developed clinical disease progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the patient may stop treatment. Symptoms of clinical disease progression must be documented in the patient's source documents and must be reported as AEs. Every effort should be made to document objective disease progression per RECIST 1.1 even after discontinuation of treatment.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at screening, throughout the study, and during the follow-up period. Please see Section 8 for more detailed discussion of efficacy evaluations.

Note that patients who discontinue without documented disease progression per RECIST 1.1 should continue to undergo tumor assessments/scans according to the Schedule of Events until PD per RECIST 1.1 is documented, new anticancer therapy is initiated, the study is terminated, or consent is withdrawn.

Once disease progression per RECIST 1.1 is confirmed or the first subsequent new anticancer therapy is initiated, whichever occurs first, the survival follow-up period begins. During this period, the patient or family should be contacted for survival follow-up every 12 weeks (±2 weeks) until withdrawal of consent, death, or loss to follow up, until study completion.

6.1.4. Ophthalmological Examination

The cornea and conjunctiva are readily visible tissues, and therefore, abnormalities of the cornea and conjunctiva can usually be recognized via external ocular examination and routine slit lamp biomicroscopy. The retina is visible through fundoscopy after dilation of the pupil. Ophthalmologic examination will be performed at screening and 4-6 weeks after first dose; additional on-study evaluation as needed due to local requirements, physician judgment, and/or symptoms or signs of mineral deposits.

Each evaluation will encompass:

1. External ocular examination
2. Routine slit lamp biomicroscopy of anterior ocular structures, including the anterior and posterior chambers (Fluorescein or rose Bengal or other dyes used to evaluate the ocular surface can be used according to institutional guidelines and local clinical practice)
3. Dilation of the pupil with direct/indirect fundoscopy per institutional guidelines and local clinical practice

6.1.5. Laboratory Assessments

All laboratory assessments will be performed locally. The laboratory must provide normal reference ranges for hematology, chemistry and coagulation tests. Laboratory results for hematology, chemistry, and coagulation assessments must be reviewed for clinically significant events. Any clinically significant events must be followed and reported as required by the protocol (please see Section 9.1.2).

- **Hematology assessments include:** Red blood cell count, hemoglobin, hematocrit, platelets, WBC count with differential (ANC, lymphocytes, monocytes, eosinophils, basophils)
- **Coagulation assessments include:** Prothrombin time-international normalized ratio, activated partial thromboplastin time, fibrinogen
- **Chemistry (serum or plasma) assessments include:** AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, lactate dehydrogenase, inorganic phosphorus, triglyceride, total cholesterol, creatinine, urea or blood urea nitrogen, sodium, potassium, chloride, calcium (corrected value), magnesium, blood glucose, creatinine clearance

  For a calculated creatinine clearance (Ccr) value, use the Cockcroft-Gault formula:

  Male Ccr (mL/min) = Body wt (kg)×(140-age)[72×serum creatinine (mg/dL)]

  Female Ccr (mL/min) = male Ccr×0.85

6.1.6. Safety Evaluations

For a detailed description of safety data collection, please refer to Section 9.

6.1.7. Pharmacokinetic and Pharmacodynamic Evaluations

For detailed discussion of PK and pharmacodynamic evaluations planned in this study, please refer to Section 7.

6.1.8. Crossover Evaluations

Patients who crossover should undergo all assessments in Table 1 for patients receiving futibatinib, including efficacy, safety, and PK assessments. Frequency of assessments should follow the schedule in Table 1 as if the patient were newly enrolled. In particular:

- Radiographic assessments of disease should be performed 2 cycles (± 7 days) up to Cycle 4 of the crossover period and every 3 cycles (± 7 days) thereafter.
- Hematology, coagulation, and serum chemistry assessments should be performed within 24 hours prior to treatment on D1 of each cycle of the crossover period, and prior to treatment on D8 and D15 of the first crossover cycle.

7. PHARMACOKINETICS

The PK population will consist of all patients who received futibatinib and have evaluable blood samples for analyses. The blood samples will be used to determine plasma futibatinib concentrations. PK data analysis is described in Section 11.5.5.

Blood samples for Pop PK analysis will be obtained from all patients receiving futibatinib on Cycle 2, Day 1 (± 3 days), pre-dose (from -30 min to just before dose) and at 1 hour and 3 hours (±30 min) post-dose. A minimum of 1 mL of whole blood will be collected for PK analysis at each timepoint. Thus, the total blood volume collected for the PK samples will be approximately 3 mL per patient (Table 10). All 3 samples should be collected on the same day.

In case that the patient interrupts medication after the pre-dose sample is collected and restarts the treatment on C2D1 at a later date, a pre-dose sample should be collected again. The second pre-dose sample will be recorded as the pre-dose sample for C2D1. The 3 samples will be collected on C2D1 of crossover treatment from patients who receive treatment with futibatinib. Dates and times of each sample collection must be recorded. Methods of sample collection and preparation will be described in a separate Laboratory Manual.

Table 10: Pharmacokinetic Blood Sample Collection

Day of Study (Time Window)	Collection Time Point (hours) in Relation to Futibatinib Administration (Time Window)	Blood Volume
Day 1 of Cycle 2 ± 3 days	pre-dose (From -30 min to just before dose)	1 mL
	1 h ± 30 min post-dose	1 mL
	3 h ± 30 min post-dose	1 mL
Total volume per patient		**Approximately 3 mL**

8. EFFICACY EVALUATIONS

8.1. Efficacy Criteria

The determination of antitumor efficacy will be based on the results of objective tumor assessments/scans interpreted by the ICR (primary analysis) and Investigator, according to RECIST 1.1.

8.1.1. Method of Imaging

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at each assessment timepoint. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of treatment. All measurements should be recorded in metric notation using a ruler or calipers.

Contrast-enhanced CT scans or MRIs are the preferred methods for tumor assessments. If a contrast agent is contraindicated in a patient, obtain a non-contrast chest CT and enhanced MRI of the abdomen (and pelvis if clinically indicated). A spiral CT should be performed using a ≤5 mm contiguous reconstruction algorithm. Images must be acquired of the chest and abdomen (and pelvis if clinically indicated or obtained at Baseline) at each time point. Only CT scans and MRI may be used for tumor measurement.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Ultrasound should not be used to measure tumor lesions that are clinically not easily accessible for overall response evaluation (eg, visceral lesions). Ultrasound is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

For additional guidance, refer to RECIST 1.1 specifications for standard anatomical radiological imaging.

8.1.2. Tumor Definitions

Measurable Lesions: Only measurable lesions can be selected as target lesions.

- Measurable visceral lesions: Lesions that can be accurately measured in at least 1 dimension with the longest diameter (to be recorded) ≥10 mm by CT scan if using slice thickness of ≤5 mm, or at least double the slice thickness of the CT or MRI scan if the slice thickness is >5 mm.
- Measurable pathological lymph nodes: A malignant lymph node must be considered pathologically enlarged with high suspicion of metastasis and measure ≥15 mm in the short axis when assessed by CT scan. The short axis is defined as the longest linear dimension perpendicular to the node's longest diameter as assessed within the same plane that the scan was acquired.

Non-measurable Lesions: All non-measurable lesions can only be selected as non-target lesions.

- Small visceral metastatic lesions that have a longest dimension <10 mm, or if slice thickness is >5 mm, less than twice the slice thickness
- Abnormal and suspected metastatic lymph nodes that are ≥10 mm to <15 mm in the short axis
- Truly non-measurable lesions (eg, ascites and peritoneal carcinomatosis)

Target Lesions:

- All measurable lesions up to a maximum of 2 lesions/organ and 5 lesions in total, representative of all involved organs/tissues should be identified as target lesions
- Target lesions should be selected on the basis of their size (visceral lesion with the longest diameter and lymph node with the measurement of short axis), be representative of all involved organs/tissues, but in addition should be those that lend themselves to reproducible repeated measurements
- When recording tumor measurements, the longest diameter will be measured for each non-nodal target lesion. For measurable pathological lymph nodes that may be identified as target lesions, the short axis measurement will be combined with the measurements of non-nodal (ie, visceral lesion) target lesions. Therefore, in cases of CR when abnormal nodes have been used as target lesions, the sum of diameters will not reduce to a null value.
- Target lesions will be followed up and measured at each subsequent timepoint. If a target lesion disappears, the tumor measurement will be captured as zero.
- The sum of the diameters for all target lesions will be calculated and recorded. The baseline sum will be used as a reference to further characterize any objective tumor assessment in the measurable dimension of the disease.
- Assign a measurement to all target lesions regardless of size. An option of "too small to measure" will be provided if a measurement cannot be assigned. A value of zero should only be assigned in the case of a CR.
- An option of "not assessable" for a lesion will only apply to lesions that cannot be read due to technical reasons including:
  - CT artifact
  - Patient positioning where the lesions are obstructed or cannot be seen
  - Lesions that may not be seen in their entirety due to CT slice thickness
- In cases where a lesion divides into 2 lesions, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- In cases where 2 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."

Non-target Lesions:

- Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions.
- The primary lesion should always be classified as a non-target lesion irrespective of its size and whether or not it can be accurately measured.
- Lymph nodes that have a short axis <1 mm are considered non-pathological and should not be recorded.
- Any equivocal lesion without clear diagnosis (eg, uncharacteristic solitary lung nodule without biopsy, uncharacteristic thyroid mass lesion without fine needle aspiration) may be considered a non-target lesion if it cannot be differentiated from a benign lesion.
- 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, but their presence, absence, or unequivocal progression should be followed throughout the study.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (eg, multiple enlarged pelvic lymph nodes or multiple liver metastases).

8.2. Efficacy Endpoints

The efficacy evaluation criteria described above will be used to derive the following primary and secondary efficacy endpoints (Table 11). Definitions of each endpoint are provided in Section 11.5.2.

Table 11: Efficacy Endpoints

Primary	Secondary
PFS by ICR	ORR and DCR (by ICR)
	OS
	PFS by Investigator assessment

Abbreviations: DCR=disease control rate; ICR=independent central review; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

8.2.1. Response Criteria

Efficacy evaluation will include the assessment of target and non-target tumor responses as well as objective responses. Responses will be assessed as defined in the Statistical Analysis Plan (SAP).

8.2.1.1. Target and Non-Target Response Assessments

Assessments will be based on the definitions for target and non-target lesions described in Table 12.

Table 12: Target and Non-target Lesions

TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, referencing the smallest sum diameters while on study.
NON-TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10-mm short axis)
Partial Response (PR)	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 of existing non-target lesions (see following definition).

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

Progression in Non-target Disease: There must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

8.2.1.1.1. Additional Criteria to Consider When Making Tumor Response Assessments

Because worsening in non-target disease cannot be easily quantified, 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 (ie, an increase in tumor burden representing an additional 73% increase in "volume" [which is equivalent to a 20% increase in the diameter of a measurable lesion]).

When effusions are known to be a potential adverse effect of treatment, cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is not mandatory, but might be performed to differentiate between response (or SD) and PD when substantial change of effusion and or ascites is noted.

If a patient is discontinued from the study before PD occurs and receives local or regional palliative radiotherapy during the follow-up period, the irradiation site must be omitted from the response assessment of the patient; however, if the site is observed to demonstrate disease progression, this case should be judged as PD.

For equivocal findings of progression (eg, 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.

8.2.1.2. Objective Response Assessment

Assessments will be based on the definitions provided in Table 13 and Table 14.

Table 13: Time Point Response for Patients with Target (±Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Objective Response
CR	CR	No	CR
CR	Non-CR/Non-PD or Not all 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

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

Table 14: Time Point Response for Patients with Only Non-target Disease

Non-Target Lesions	New Lesions	Objective Response
CR	No	CR
Non-CR/Non-PD	No	SD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

9. SAFETY EVALUATIONS

9.1. Adverse Events

9.1.1. Definitions of Adverse Events

An AE is any untoward medical occurrence in a clinical study patient and does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

All AEs will be collected from the time the main ICF is signed through 30 days after the last dose of any study therapy (safety follow-up) or until the start of new antitumor therapy, whichever is earlier. For all AEs that occur between signing the pre-screening consent and main study ICF, there is no need to record those that are unrelated unless it is mandatory by local regulations. All AEs will be documented in the eCRF. Any untoward medical event that occurs after the safety follow-up is not considered an AE, unless the Investigator considers that the AE is related to the study drug. Serious AEs related to study therapy will be collected through the survival follow-up.

All AEs will be documented in the eCRF. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event.

Signs and symptoms of a pre-existing disease should not be considered an AE, but should rather be considered baseline signs and symptoms. Clinically significant worsening of pre-existing signs and symptoms is considered an AE.

For definitions and reporting of pregnancies, overdoses, and medication errors, refer to Section 9.4.1, Section 9.4.2, and Section 9.4.3, respectively.

9.1.2. Reporting of Adverse Events

9.1.2.1. Terms of Reported Adverse Events

All AEs will be documented in the eCRF according to the eCRF Completion Guidelines. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event. However, all SAEs must be reported on an SAE form as per the SAE form completion guidelines, as well as in the eCRF.

When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms or signs, as the AE(s).

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

9.1.2.2. Severity of Adverse Events

The NCI-CTCAE Version 5.0 will be used to grade the severity of AEs.

9.1.2.3. Causal Relationship with Study Drug

The causal relationship between an AE and the study drug will be assessed using the following 2-point scale, taking into account the patient's condition, medical history, concomitant medications, and the temporal relationship between study drug administration and onset of the AE.

1. An AE is considered to be "**Related**" if the event follows a reasonable temporal sequence from administration of study drug and there is a **reasonable possibility** that at least one of the following conditions is true:
    - A positive dechallenge: This means that the event improves or resolves after the drug is stopped (temporarily or permanently).
    - A positive rechallenge: This means that the event reappears after the drug is restarted.
    - The event cannot be reasonably explained by the patient's clinical state and/or other therapies administered.
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson syndrome).
2. An AE is considered to be "**Not related**" if there is **no reasonable possibility** that:
    - The event occurred prior to study drug administration.
    - There is no reasonable possibility that the study drug caused the event.
    - The event does not follow a reasonable temporal sequence from administration of study drug and could have been produced by a documented pre-existing condition, concomitant medication or patient's clinical state.

For the purposes of safety reporting, "no reasonable possibility" means there is no evidence to suggest a causal relationship between the study drug and the AE.

9.1.2.4. Outcome of Adverse Events

Record the outcome of AEs as follows:

1. Resolved
2. Not resolved
3. Fatal

9.1.2.5. Follow-up of Adverse Events

Any ongoing AEs should be followed until the earliest occurrence of one of the following:

- The AE has resolved or stabilized
- Completion of Safety Follow-up visit

- Start of new antitumor therapy
- Withdrawal of consent
- Death
- Other (eg, transfer to another hospital)

9.2. Laboratory Assessments

9.2.1. Reporting and Evaluation of Laboratory Test Results

All laboratory results must be reviewed by the Investigator. A new laboratory or instrumental abnormality that has a clinical impact on a patient (including eg, resulting in study drug dose reduction, treatment delay, treatment discontinuation or requirement of intervention) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE.

All laboratory values that are out of the normal range are to be evaluated for their clinical impact before exposing the patient to the next dose of futibatinib.

The NCI-CTCAE Version 5.0 will be used to grade the severity of laboratory data.

9.2.2. Repeat Testing

Evaluation of any clinically significant laboratory test will be repeated, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until another treatment is given.

9.3. Serious Adverse Events

9.3.1. Definitions of Serious Adverse Events

A SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;

  The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization to treat the AE.

  The following are not considered hospitalizations for the purposes of assessing seriousness:

  – Emergency room visits < 24 hours;

  – Hospitalizations for preplanned procedures;

  – Hospitalization for study-related treatment and procedures.

- Results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment.
- Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).
- Is any other important medical event that based upon appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above (eg, may not result in death, be life-threatening, or require hospitalization). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

9.3.2. Reporting of Serious Adverse Events (within 24 hours)

All SAEs occurring from the time the ICF is signed through the Safety Follow-up Period (30 days after the last dose of study drug or discontinuation of the Safety Follow-up Period, whichever is earlier) must be reported to Sponsor's Pharmacovigilance group or its designee **within 24 hours** from the time the Investigator first becomes aware of the SAE.

Comprehensive information available at the time of initial reporting (including narrative description, medical history, and concomitant medications) needs to be provided with careful consideration regarding causality and serious criterion. The SAE reporting process and contact information are provided in supplement guidelines.

After the initial SAE notification to the Sponsor's Pharmacovigilance group or its designee, all follow-up SAE information will be submitted each time they become available (for example, clinical diagnosis, outcome, causality assessment, results of specific investigations) on a follow up SAE form.

The investigator also must submit further information if it is required by the Sponsor or the director of the study site or an institutional review board (IRB)/independent ethics committee (IEC). Every SAE should be followed until it has resolved, stabilized, or returned to baseline.

9.3.3. Reporting of Deaths (within 24 hours)

All deaths occurring from the time the ICF is signed through the Safety Follow-up Period (30 days after the last dose of study drug or discontinuation, whichever is earlier) must be reported within 24 hours from the time the Investigator first becomes aware of the death. The primary cause of the death should be reported as the SAE term, if available.

When reporting a death, site personnel will be required to identify which of the following best describes the category for cause of death:

- Toxicity caused by study drug
- Radiographic disease progression
- Clinical disease progression
- Other causes

9.4. Other Safety Information

9.4.1. Pregnancy

If a patient becomes pregnant while on study treatment or within 30 days following the last dose of study therapy, the study treatment must be immediately discontinued if ongoing. Pregnancy information in a female patient (or for the female partner of a male patient) should be reported **as soon as possible** from the time the Investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a paper Pregnancy Form and faxing or e-mailing it to Sponsor's Pharmacovigilance group or its designee.

New and/or corrected information regarding the pregnancy obtained after submitting the Pregnancy Form must be submitted on an updated Pregnancy Form to the Sponsor's Pharmacovigilance group or its designee. Pregnancies must be followed to outcome by the Investigator, even after study completion.

If the outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, it should be reported as a SAE to the Sponsor's Pharmacovigilance group or its designee. Live births will be followed up by the Investigator. Any information that may be associated with the study drug should be reported even after study completion.

9.4.2. Overdose

An overdose for this clinical study is defined as taking or receiving an intentional or unintentional dose of futibatinib, gemcitabine, or cisplatin beyond the recommended dose for 1 day or beyond the recommended total dose in each cycle.

An overdose of study therapy should be reported to the Sponsor's Pharmacovigilance group or its designee within 24 hours from the time the Investigator first becomes aware of the overdose, whether or not it was accidental or intentional, and whether or not the patient developed an AE (even if not fulfilling a seriousness criterion).

There is no known antidote available in case of futibatinib overdose. Overdose should be managed with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

9.4.3. Medication Errors

A medication error is defined as any unintentional error in prescribing, dispensing, or administering the study drug while the study drug is in the control of the healthcare professional or patient.

The following types of medication errors, regardless of whether it is associated with an AE or SAE, should be reported to the Sponsor's Pharmacovigilance or designee within 24 hours from the time the Investigator first becomes aware of its occurrence:

- Medication errors with study medication or concomitant medication resulting in an AE
- Medication errors with study medication resulting in an overdose
- Incorrect route of study medication administration
- Administration of the incorrect study medication

Note: Medication errors with the study medication that result in the omission of an administration, an incorrect dose, or the administration of more than the prescribed dose (but does not meet the overdose criteria), will not be reported as a SAE, but will be identified through the recording of study drug accountability data in the eCRFs.

10. ANALYSES OF BIOMARKERS

10.1.1. Objectives and Background

All biomarker assessments described in this section will be performed at the timepoints shown in the Schedule of Events (Table 1); methods of sample collection and preparation will be described in a separate Laboratory Manual.

The pharmacodynamic biomarker population will consist of all patients who received futibatinib or gemcitabine-cisplatin and have evaluable pharmacodynamic biomarker data. Detailed analytical procedures will be described in the SAP.

10.1.2. Assessment of *FGF/FGFR* Aberrations in Blood

A blood sample will be collected to assess *FGF/FGFR* aberrations in circulating tumor DNA (ctDNA) prior to the first futibatinib administration on Day 1 of Cycle 1, and at the EOT visit or time of progression. In addition to assessing ctDNA as a pharmacodynamic biomarker, samples, or a set of samples, will be used to verify its utility as an alternative to tumor tissues for the potential companion diagnostic. Samples will be collected and stored, as per the Laboratory Manual, and analyzed in batches.

10.1.3. Measurement of Tumor Marker CA19-9

Blood samples will be collected for measurement of circulating tumor marker CA19-9 during screening and in conjunction with tumor assessments/scans throughout the study.

10.1.4. Tumor Samples

Archival or fresh tumor biopsy samples will be collected to confirm *FGFR* gene status at the Sponsor's designated central laboratories. The remaining samples may be stored at the Sponsor's designated central laboratories for up to 10 years after study completion for future testing.

11. STATISTICS

The statistical analysis methods will be documented in detail in the SAP.

11.1. Estimation of Sample Size

Assuming median PFS of 10 months in the Experimental Arm and 6 months in the Control Arm, a total of 162 PFS events will be needed to detect a hazard ratio of 0.60 with 90% power at a 2-sided alpha level of 0.05.

Considering an enrollment rate of 4 patients per month in the first 10 months and 8 patients per month from Month 11 to Month 32, approximately 216 patients with iCCA harboring centrally confirmed *FGFR2* gene rearrangements are planned to be randomized in 1:1 ratio to the Experimental Arm and Control Arm. It is estimated that 162 PFS events would occur approximately 40 months (32-month enrollment period and 8-month follow up period) after the start of randomization. These calculations further assume a 10% loss to follow-up annually.

11.2. Planned Interim Analysis

No interim analysis of efficacy is planned. Interim analyses for safety monitoring will occur when approximately 25%, 50%, and 75% of the planned total number of patients have been treated. A DMC will meet to assess the cumulative safety data and recommend study continuation, discontinuation, or study modification. A description of the roles and responsibilities of the DMC and details of the review processes are provided in a separate DMC charter.

11.3. Analysis Populations

The analysis study populations in this study are defined in Table 15.

Table 15: Analysis Populations

Analysis Population	Definition
All Enrolled Population	All patients who sign a main study ICF (including screen failures).
All Randomized Patients / Full Analysis Dataset	All patients randomized to any treatment group in the study. This is the primary population for analyses of demography, protocol deviations, baseline characteristics and efficacy.
All Treated Population / Safety Analysis Dataset	All patients who received at least one dose of study drug. This is the primary population for dosing and safety analyses.
Per-Protocol Patients / Per-Protocol Analysis Dataset	All randomized patients who have no relevant protocol deviations. For patients who have a relevant deviation during the study, data collected before the point of deviation will be included in the analysis preformed for this population. This is the population for efficacy sensitivity analysis.
Pharmacodynamic / Biomarker Evaluable Set	All patients in the All Treated Population who have evaluable pharmacodynamic/biomarker data for analyses.
Pharmacokinetic Evaluable Set	All patients who received futibatinib and have evaluable plasma data for analysis.

Abbreviations: ICF=informed consent form

The treatment group As Randomized will be retrieved from the IXRS system. The treatment group As Treated will be the same as the arm randomized by IXRS. However, if a patient received the incorrect drug for the entire period of treatment, the patient's treatment group will be defined as the incorrect drug the subject actually received.

11.4. Criteria for Handling of Patient Data

The criteria for handling of patient data are provided in the Statistical Analysis Plan (SAP).

11.5. Statistical Analyses

11.5.1. Demographic and Baseline Characteristics

The number of patients in each study population and the reasons for exclusion will be summarized. In each analysis population, the distribution of main patient background, disease characteristics, and baseline laboratory values and clinical findings will be summarized. These patient attributes will be summarized using frequency distribution or descriptive statistics as appropriate.

11.5.2. Efficacy Analyses

A description of each efficacy endpoint is provided in Table 16. Response assessments will be made based on RECIST 1.1; the primary evaluation of endpoints will be based on ICR except as otherwise noted. Efficacy analyses will be performed in all randomized population by As Randomized treatment group unless otherwise specified. See the SAP for more detailed information on the efficacy analyses.

Table 16: Efficacy Endpoint Definitions

Endpoint	Definition
PFS	Time from date of randomization to the date of documentation of disease progression, or date of death, whichever occurs first
ORR	Proportion of patients experiencing a best overall response of PR or CR (per RECIST 1.1).
DCR	Proportion of patients experiencing a best overall response of SD, PR, or CR (per RECIST 1.1).
OS	Measured from the date of randomization until the date of death due to any cause.
DOR	Time from the first documentation of response to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
PFS2	Time from randomization to subsequent disease progression per ICR after initiation of next-line therapy or death from any cause (whichever occurs first).

Abbreviations: CR=complete response; DCR=disease control rate; DOR=duration of response; ICR=independent central review; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival on next-line therapy; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

11.5.2.1. Primary Efficacy Analysis

Comparison of PFS (per ICR) between arms will be performed when at least 162 PFS events have been observed. The comparison will test the null hypothesis:

H_0: PFS in experimental arm = PFS in control arm,

against the alternative hypothesis:

H_1: PFS in experimental arm $\neq$ PFS in control arm.

The difference in PFS will be compared by stratified log-rank test at 2-sided α=0.05. The tests will be by the stratification factors used in the randomization. The hazard ratio and the corresponding 95% CIs will be estimated using the Cox regression model stratified by the same stratification factors. The median PFS, and the PFS rates at 6, 12 and 18 months, will be calculated using the Kaplan-Meier (KM) product-limit estimates for each treatment arm, and presented with 2-sided 95% CIs. The KM estimates of PFS will be plotted over time. The PFS censoring rules and definition of progression date will follow the Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)."

11.5.2.2. Secondary Efficacy Analyses

The fixed sequence procedure will be used to control the overall type I error rate of analyses for the secondary endpoints at $\alpha = 0.05$ (2-sided) after the superiority for primary efficacy endpoint, PFS, is declared. The order of testing for secondary endpoints will follow the order that they are presented below.

In the ordered sequence, each secondary endpoint will be tested at the 5% level until the first nonsignificant outcome occurs. If the first nonsignificant outcome occurs, then the results of the analysis of the subsequent endpoints will be presented for descriptive purposes only.

1. ORR

ORR will be calculated for each treatment arm with exact 95% CIs using the method of Clopper and Pearson. The analysis of ORR for comparison between treatment arms will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by the stratification factors used in the randomization.

2. DCR

DCR will be calculated for each treatment arm with exact 95% CIs using the method of Clopper and Pearson. The analysis of DCR for comparison between treatment arms will be performed using the CMH test stratified by the stratification factors used in the randomization.

3. OS

OS will be evaluated using KM estimates and the comparison in OS between the two arms will use a stratified log-rank test with the randomization stratification factors. The corresponding estimate of the hazard ratio calculated from Cox proportional hazard model with treatment group as a factor and stratified by the randomization stratification factors, will be presented with a 2-sided 95% CI.

No multiplicity adjustments will be used for other secondary efficacy endpoints.

11.5.2.3. Exploratory Efficacy Analyses

Analysis of exploratory endpoints will be discussed in a separate SAP.

11.5.3. Safety Analyses

The safety analysis will be performed using the All-Treated Population, by As-Treated group.

AEs will be coded according to the Medical Dictionary for Regulatory Activities terminology and the severity of the toxicities will be graded according to the NCI-CTCAE (Version 5.0), where applicable.

Concomitant medications will be coded according to the World Health Organization Drug Dictionary for Concomitant Medication.

All AEs reported from the date of first dose of study therapy through 30 days after the last dose of study therapy will be summarized by System Organ Class, Preferred Term, toxicity/severity grade, and causal relationship to futibatinib. In addition, separate summaries of SAEs, deaths, and Grade 3 or 4 AEs will be presented.

By-patient listings of preferred AE terms, grade, onset date, action, outcome of AE, and causality will be provided. Hematological and chemistry laboratory parameters will be graded according to the NCI-CTCAE (Version 5.0) where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized. Safety data (AEs and clinical laboratory results) will be summarized descriptively. A list of 12-lead ECG findings will be presented by patient.

11.5.4. Pharmacodynamic/Biomarker Analysis

The exploratory pharmacodynamic/biomarker endpoints are described in Section 10. Analyses will be performed using all patients in the All Treated set who have evaluable data for pharmacodynamic/biomarker analyses. Pharmacodynamic and biomarker data will be summarized descriptively, and the exploratory analyses of the relationship between biomarker and PK, efficacy or toxicity will be performed.

11.5.5. Pharmacokinetic Analysis

The concentration vs. time data obtained in this study will be combined with data from other studies in the clinical development program to develop a Pop PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of futibatinib and to estimate measures of individual exposure (such as steady-state peak, trough and area under the plasma drug concentration-time curve). Model estimated exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. The results of Pop PK and exposure response analyses will be reported separately.

11.5.6. PRO Analyses

A separate pre-specified PRO analysis following FDA and European Medicines Agency PRO Guidelines will be performed and detailed in a separate SAP and PRO report. Scoring of PRO instruments and derivation of utility for health economic analysis will also be described in a separate analysis document.

12. ADMINISTRATIVE CONSIDERATIONS

12.1. Protocol Compliance

The Investigator will agree to comply with the protocol by signing the Declaration of Investigator . In the event that the Investigator is unable to continue the study and another suitable person is designated as the Investigator, the Sponsor must be notified in advance (30 days prior notice is requested). The new Investigator must accept the responsibility in writing and be approved by the Sponsor and the IRB/IEC.

12.2. Protocol Deviations

The Investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study patients without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change and the reasons for it should be documented and submitted to the IRB/IEC and Sponsor.

The Investigator is to record any deviation from the protocol in the source documents, describing this departure and the circumstances under which it was required.

12.3. Protocol Amendments

All protocol amendments must be issued by the Sponsor, and signed and dated by the Investigator. Documentation of amendment approval by the Investigator and IRB/IEC must be provided to the Sponsor.

If the changes involve only logistic or administrative aspects of the study, these changes will be notified in writing by the Sponsor.

12.4. Study Termination

If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. The Sponsor also reserves the right to discontinue this study for administrative or discretionary reasons at any time.

12.5. Case Report Forms

The Investigator should complete all eCRFs in accordance with the eCRF Completion Guidelines. Data in the eCRFs shall be consistent with source documents.

In this study, the Investigator and assigned personnel will be given access to the EDC system; passwords should not be shared. Data managers and Monitors will have the right to access the EDC system for performing source data verification. Data managers will have the right to access the EDC system as appropriate for their roles. Other relevant personnel may receive access to view EDC data.

An eCRF should be completed for each screened and enrolled patient (patients who are pre-screened only do not require an eCRF).

After verification of the eCRFs, the Sponsor or designee may query discrepancies or request additional information. The Investigator, or assigned personnel, should verify the data and correct as necessary prior to approval of the eCRFs.

12.6. Access to Source Data/Documents

The Investigator or designated study personnel must make all study-related records available for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

12.6.1. Source Data/Documents

Source documents are original documents, data, and records such as hospital records, clinical and office charts, laboratory notes, memoranda, patient's evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfilm or magnetic media, X-ray, patient files, and records kept at the pharmacy, laboratories, and medical-technical departments involved in the study.

Specific details regarding source documents and source data to be recorded directly on the eCRFs for the study should be identified with the Investigator prior to and during the study.

12.6.2. Access to Source Data

The Sponsor's study monitor, or other representatives, should verify the entries in the eCRF and source documents to confirm the completeness and accuracy of the data. If there are any discrepancies between the entries in eCRFs and source documents, the monitor will query the site.

12.7. Data Handling

All study information is confidential. The patient's and Investigator's personal data which may be included in the Sponsor's database shall be treated in compliance with all applicable laws and regulations.

When processing and archiving personal data pertaining to the Investigator and to the patients, the Sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

12.8. Responsibilities of Recordkeeping

12.8.1. Investigator and Study Site

The Investigator and the study site are responsible for the retention of all study documents according to institutional policies, local laws, and International Conference on Harmonisation (ICH) E6 Guideline.

The Investigator and the study site agree to inform the Sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting the Sponsor, the Investigator and study site must ensure that the applicable regulatory requirements have been satisfied. The Sponsor will evaluate the requests from the Investigator and the study site and will provide authorization for destruction of such records in writing.

In the event that all retention of records requirements have been fulfilled, but the Sponsor requests that the Investigator and study site maintain the records for a longer period of time, additional arrangements will be made.

12.8.2. Sponsor

The Sponsor must retain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements of the countries where the product is approved, and where the Sponsor intends to apply for approvals.

If the Sponsor discontinues the clinical development of the study drug, the Sponsor must maintain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements.

12.9. Monitoring

The Sponsor and designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

12.10. Financial Disclosure

Financial disclosure for Investigators will be obtained and record keeping of financial records will be in accordance with local regulatory requirements. Investigators will provide the Sponsor with sufficient, accurate financial information upon the Sponsor's request.

12.11. Compensation for Health Injury

The clinical study is insured according to applicable regulatory requirements. A copy of the Compensation Policy Document will be provided to the study site by the Sponsor. In the case of a compensation claim, excluding claims that have arisen due to medical malpractice or negligence, the legally responsible person is clearly identified. Sponsor should address the policies and payment procedures of compensation for the event of study-related injuries as the Compensation Policy Document. When patients receive compensation, the policies and payment procedure of compensation should comply with the Compensation Policy Document.

12.12. Study Administrative Structure

The study organization details will be maintained in a supplement.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will perform quality control and quality assurance procedures in accordance with the Sponsor's standard operating procedures (SOPs) to ensure the quality of the clinical study.

13.1. Quality Control

The Sponsor is responsible for controlling the quality of the clinical study according to the SOPs regarding, for example, study operation, monitoring, data collection and management, statistical analysis, and handling of safety information to verify that the study-related activities have been fulfilled.

13.2. Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical study.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to ensure that these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6 guidelines, and any applicable local regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

Any results arising from such inspections will be immediately communicated by the Investigator to the Sponsor. The Investigator and the Sponsor will take corrective actions for all findings and observations found during audits and/or inspections. The auditors and inspectors will not disclose private information unless required by law.

14. ETHICS

14.1. Ethical Conduct of the Study

It is mandatory that all considerations regarding the protection of patients be carried out in accordance with the latest versions of the protocol, ICH GCP Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

14.2. Written Informed Consent

The ICF(s) must be approved by the IRB/IEC before a patient signs consent for any study-related activity. It must be in a language that the patient can read and understand. The ICF process should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, and applicable regulatory requirements. Each patient (or a legally acceptable representative) must give written consent according to local requirements.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

There must be documentation in each patient's case history/medical record that informed consent was obtained prior to any study procedure being performed. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

14.3. Institutional Review Board/Independent Ethics Committee

The study must be approved by an appropriately constituted IRB/IEC, as required in the applicable local regulation such as ICH E6 Guidelines (Part 3), Code of Federal Regulations Title 21, part 56, and Ordinance of the Ministry of Health and Welfare No. 28, Chapter IV, Section 1 before the study is initiated. At the end of the study, the Investigator will notify the IRB/IEC of the conclusion of the study and its outcome.

15. PUBLICATION POLICY

15.1. Publication Policy

The Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country or region.

The results of the study may be presented during scientific symposia and/or published in a scientific journal only after review by the Sponsor in accordance with the guidelines set forth in the applicable publication or financial agreement.

The Investigators and the Sponsor will discuss and determine the presenter(s) or author(s) and timing of any presentation or publication related to this study and/or its results. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

15.2. Secondary Use of Data

The Sponsor maintains the right to secondary use of data in this study.

Secondary use of data describes the use of data from this study for other study/studies for purposes including, but not limited to, drug development and/or academic research. Secondary use of data also includes external offerings of study data to domestic and/or foreign organization(s) and researcher(s), on a case by case basis.

16. REFERENCES

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APPENDIX A. ECOG PERFORMANCE STATUS

GRADE	ECOG
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

From: Oken et al. 1982

APPENDIX B. DIETARY GUIDELINES FOR TREATMENT OF HYPERPHOSPHATEMIA

The best way to limit phosphorus in the diet is to limit foods highest in phosphorus, including:

- Fast food, convenience foods, and processed foods, which may be full of phosphorus additives
- Beverages that contain phosphorus (look for the letters "phos" in the ingredient list)

Also, look for any ingredient that contains "phos" in the term such as:

- Calcium phosphate
- Disodium phosphate
- Phosphoric acid
- Monopotassium phosphate
- Sodium acid pyrophosphate
- Sodium tripolyphosphate

Listing of Some Lower and Higher Phosphorus Foods	
Higher Phosphorus Foods	**Lower Phosphorus Foods**
Milk, pudding, yogurt, soy milk, nondairy creamers and enriched rice milk	Unenriched rice milk
Processed cheeses and cheese spreads	A small amount of Brie or Swiss cheese
Hard cheeses, ricotta or cottage cheese, fat-free cream cheese	Regular or low-fat cream cheese
Ice cream or frozen yogurt	Sherbet, sorbet or frozen fruit pops
Soups made with higher phosphorus ingredients (milk, dried peas, beans, lentils)	Soups made with lower phosphorus ingredients (broth- or water-based with other lower phosphorus ingredients)
Whole grains, including whole-grain breads, crackers, cereal, rice and pasta	White bread, crackers, cereals, rice and pasta
Quick breads, biscuits, cornbread, muffins, pancakes or waffles	White dinner rolls, bread, bagels or English muffins
Dried peas (split, black-eyed), beans (black, garbanzo, lima, kidney, navy, pinto) or lentils	Green peas, green beans or wax beans
Processed meats (ie, bologna, ham and hot dogs), and meat, poultry or seafood with "phos" in the ingredients	All-natural lean beef, pork, lamb, poultry, seafood or other fish without "phos" in the ingredients
Organ meats, walleye, pollock or sardines	All-natural lean beef, pork, lamb, poultry, seafood or other fish without "phos" in the ingredients
Nuts and seeds	Popcorn or pretzels
Peanut butter and other nut butters	Jam, jelly or honey
Chocolate, including chocolate drinks	Jelly beans, hard candy, fruit snacks or gumdrops
Colas and pepper-type sodas, some flavored waters, bottled teas, some drink mixes (any with "phos" in the ingredients)	Lemon-lime soda, ginger ale, root beer, plain water or some drink mixes (any without "phos" in the ingredients)
Although a food or drink may be low in phosphorus, limitation of portion size and the number of servings you eat or drink each day may still be recommended.	

From: Rachael Majorowicz, R.D.N., L.D. (Feb, 2016). Why is a low-phosphorus diet useful in managing kidney disease? What foods contain phosphorus? https://www.mayoclinic.org/food-and-nutrition/expert-answers/faq-20058408.

APPENDIX C. CLASSIFICATION OF SUBSTRATES, INHIBITORS, AND INDUCERS OF CYP ENZYMES AND TRANSPORTERS

The classification below is based on the FDA Draft Guidance for Industry, Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications, October 2017. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

CYP3A inhibitors and inducers: CYP3A is involved in the metabolism of futibatinib. CYP3A inhibitors and inducers may alter the concentration and activity of futibatinib.

CYP3A substrates: Futibatinib is a potential time-dependent inhibitor of CYP3A. Futibatinib may increase the concentration and activity of CYP3A substrates.

P-gp substrates and BCRP substrates: Futibatinib is a potential inhibitor of P-gp and BCRP. Futibatinib may alter the concentration and activity of P-gp and BCRP substrates.

P-gp inhibitors and BCRP inhibitors: Futibatinib is a substrate of P-gp and BCRP. P-gp and BCRP inhibitors may alter the concentration and activity of futibatinib.

Examples of CYP3A Inhibitors		
CYP Enzyme	**Strong Inhibitors:[1] ≥ 5-fold increase in AUC or ≥ 80% decrease in CL**	**Moderate Inhibitors:[2] ≥ 2 but < 5 fold increase in AUC or 50 – 80% decrease in CL**
CYP3A	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice[3], indinavir and ritonavir, idelalisib, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

[1] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the area under concentration-time curve (AUC) of a sensitive index substrate for that CYP by equal to or more than 5-fold.
[2] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive index substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
[3] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
Abbreviations: AUC = area under the concentration-time curve; CL = oral clearance.

Example of CYP3A Inducers		
CYP Enzyme	**Strong inducers[1] or ≥ 80% decrease in AUC**	**Moderate Inducers[2] 50 – 80% decrease in AUC**
CYP3A	Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[3]	Bosentan, efavirenz, etravirine, modafinil

[1] A strong inducer is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%.
[2] A moderate inducer is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥50% to <80%.
[3] The effect of St. John's wort varied widely and is preparation-dependent.
Abbreviation: AUC = area under the concentration-time curve.

Example of CYP3A Substrates		
CYP Enzymes	**Sensitive Substrates[1]**	**Moderate Sensitive Substrates[2]**
CYP3A	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil	Alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

[1] Sensitive substrates are drugs that demonstrate an increase in area under the concentration-time curve (AUC) of ≥ 5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.
[2] Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 2 to < 5 fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.

Example of Inhibitors for P-gp and BCRP		
Transporters	**Gene**	**Inhibitor**
P-gp[1]	*ABCB1*	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP[2]	*ABCG2*	Curcumin, cyclosporine A, eltrombopag

[1] P-gp: (1) AUC fold-increase of digoxin ≥2 with co-administration and (2) *in vitro* inhibitor.
[2] BCRP: (1) AUC fold-increase of sulfasalazine ≥1.5 with co-administration and (2) *in vitro* inhibitor. Cyclosporine A and eltrombopag were also included, although the available DDI information was with rosuvastatin, where inhibition of both BCRP and OATPs may have contributed to the observed interaction.
Abbreviations: AUC = area under the concentration-time curve; BCRP = breast cancer resistance protein; P-gp = p-glycoprotein.

Example of Substrates for P-gp and BCRP		
Transporters	**Gene**	**Substrate**
P-gp[1]	*ABCB1*	Dabigatran, digoxin, fexofenadine
BCRP[2]	*ABCG2*	Rosuvastatin, sulfasalazine

[1] P-gp: (1) AUC fold-increase ≥2 with verapamil or quinidine co-administration and (2) in vitro transport by P-gp expression systems, but not extensively metabolized.
[2] BCRP: (1) AUC fold-increase ≥2 with pharmacogenetic alteration of ABCG2 (421C>A) and (2) in vitro transport by BCRP expression systems.
Abbreviations: AUC = area under the concentration-time curve; BCRP = breast cancer resistance protein; P-gp = p-glycoprotein.

APPENDIX D. SUPPLEMENTAL REQUIREMENTS FOR JAPAN

1. Sample Size for Japan

Expected sample size for Japan: approximately 22 patients

2. Clinical Study Period

Planned clinical study schedule: From December 2019 to April 2023

3. Effective Contraception During Study

In Section 5.5 of this protocol, the following drugs or devices for contraception (marked with asterisks [*]) are not approved in Japan:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation with an oral, intravaginal* or transdermal* form
- progestogen-only hormonal contraception associated with inhibition of ovulation with an oral, injectable or implantable* form
- In case that effective contraception methods are not general, patients should follow the authority regulations or use double-barrier method of contraception (eg, condom with pessary, condom with spermicidal jelly*, spermicide* or film*, pessary with spermicidal jelly*, spermicide *or film).