Clinical Development

Protocol QBGJ398-301

A Phase 3 Multicenter, Open-Label, Randomized, Controlled Study of Oral Infigratinib Versus Gemcitabine With Cisplatin in Subjects With Advanced/Metastatic or Inoperable Cholangiocarcinoma With FGFR2 Gene Fusions/Translocations: the PROOF Trial

Investigational Product:	Infigratinib (BGJ398)
Phase of Development	3
US IND Number:	104,187
EUDRACT number:	2018-004004-19
Protocol:	Version 4.0 (27 July 2021)
Supersedes:	Version 3.0 (15 April 2021)
Sponsor:	QED Therapeutics, Inc. 8000 Marina Blvd, Suite 400 Brisbane, CA 94005
Medical Monitor:	PPD MD Vice President, Clinical Development QED Therapeutics, Inc. PPD PPD

INVESTIGATOR'S AGREEMENT

I have read Protocol QBGJ398-301 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Printed Name of Investigator

_____

Signature of Investigator

_____

Date

_____

Study Center Number

_____

Study Center Name

Signature on this page assures the sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) operates in accordance with the governing regulations, and that the investigator understands, and agrees to abide by, all governing regulatory obligations and the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and country and regional (local) requirements while conducting this clinical investigation. Additionally, the investigator agrees to give access to all relevant data and records to the sponsor's monitors, auditors, sponsor Clinical Quality Assurance representatives, designated agents of the sponsor, IRBs/IECs/REBs, and regulatory authorities as required.

TRIAL CONTACTS

Table 1: Trial Contact Information

Role in Study	Name	Contact Information
Vice President, Clinical Development	PPD MD	email: PPD Telephone: PPD
Pharmacovigilance/ Safety Management	Covance Safety	email: SAEintake@covance.com FAX: refer to the Study Manual for country-specific FAX numbers

Abbreviations: FAX, facsimile.

PROTOCOL VERSION HISTORY

Protocol Version	Amendment Number	Date
0.0	Not applicable	04 October 2018
1.0	1.0	11 March 2019
2.0	2.0	08 October 2019
2.1	2.1	10 October 2019
2.2	2.2	02 April 2020
2.3	2.3	27 July 2020
3.0	3.0	15 April 2021
4.0	4.0	27 July 2021

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term/Definition
ADL	activities of daily living
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic-pyruvic transaminase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
AUC	area under the curve
BCRP	breast cancer resistance protein
BGJ398	infigratinib
BICC1	bicaudal c homolog 1
BICR	blinded independent central review
BOR	best overall response
CI	confidence interval
C_{max}	maximum observed plasma concentration after drug administration
C_{min}	measured concentration at the end of a dosing interval
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome p
DEB-TACE	drug eluting bead-TACE
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study

Abbreviation	Term/Definition
EOT	end of treatment
EPO	erythropoietin
EQ-5D	EuroQOL five dimensions questionnaire
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FGFR1	fibroblast growth factor receptor 1
FGFR2	fibroblast growth factor receptor 2
FGFR3	fibroblast growth factor receptor 3
FGFR4	fibroblast growth factor receptor 4
FMI	final market image
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IPCW	inverse probability of censoring weighting
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IVD	in vitro diagnostic medical devices
K-M	Kaplan-Meier
LLN	lower limit of normal
LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen activated protein kinase

Abbreviation	Term/Definition
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NaF	sodium fluoride
NCCN	National Comprehensive Cancer Network
NK-1	neurokinin-1
OCT	optical coherence tomography
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFS2	PFS on subsequent therapy
PHI	protected health information
PK	pharmacokinetics
PO	oral
PR	partial response
PT	preferred term
QD	once a day
QLQ	quality of life questionnaire
QOL	quality of life
QT	measure of time between the start of the Q wave and the end of the T wave (QT interval) in the heart's electrical cycle
QTc	QT interval corrected for heart rate
QTcF	QTc corrected by Fridericia's formula
R_{acc}	accumulation ratio calculated as C_{min} steady-state/C_{min}
RBC	red blood cell
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid

Abbreviation	**Term/Definition**
RPSFT	rank-preserving structural failure time
RPTD	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
TACE	transarterial chemoembolization
TC99	technetium-99 (^{99}Tc)
TdP	Torsades de Pointes
T_{max}	time at which the maximum observed concentration (C_{max}) occurs
ULN	upper limit of normal
UNK	unknown
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential

1 SYNOPSIS

Name of Sponsor/Company: QED Therapeutics

Name of Investigational Product: Infigratinib (formerly BGJ398, also known as BBP-831, and infigratinib phosphate)

Name of Active Ingredient: Infigratinib

Title of Study: A Phase 3 Multicenter, Open-Label, Randomized, Controlled Study of Oral Infigratinib versus Gemcitabine with Cisplatin in Subjects with Advanced/Metastatic or Inoperable Cholangiocarcinoma with FGFR2 Gene Fusions/Translocations: The PROOF Trial

Study centers: This is a multicenter study involving approximately 145 study centers worldwide.

Medical Monitor: PPD MD

Study period (years):	**Phase of development:** 3
First subject enrolled: 27 Dec 2019 Estimated date last subject completed: 3Q2024	

Objectives:

Primary: The primary objective is to determine if treatment with infigratinib improves progression-free survival (PFS) as assessed by blinded independent central review (BICR) compared to treatment with gemcitabine and cisplatin in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion/rearrangement.

Secondary: The secondary objectives are to

- Determine if treatment with infigratinib improves overall survival (OS) compared to treatment with gemcitabine and cisplatin in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion/rearrangement.
- Evaluate the efficacy of infigratinib treatment compared to gemcitabine and cisplatin in terms of investigator assessed PFS.
- Further evaluate the efficacy in subjects treated with infigratinib versus gemcitabine and cisplatin by overall response rate (ORR), best overall response (BOR), duration of response and disease control rate determined by BICR and by the investigator.
- Characterize the safety and tolerability of single agent infigratinib.

Exploratory: The exploratory objectives are to

- Evaluate the efficacy of infigratinib treatment compared to gemcitabine and cisplatin in terms of investigator assessed PFS after subsequent therapy (PFS2).
- Compare quality of life (QOL) in subjects treated with infigratinib or gemcitabine and cisplatin.
- Assess the pharmacokinetics (PK) of infigratinib and its active metabolites including BHS697 and CQM157.
- Evaluate the overall genomic landscape of subjects with cholangiocarcinoma.
- Evaluate biomarkers related to cholangiocarcinoma biology and their potential correlation to efficacy, disease progression, and resistance to study medications.

Endpoints:

Primary:

- PFS (from date of randomization until date of progression as determined by BICR or death due to any cause, whichever is earlier)

Secondary:

- OS (from date of randomization until date of death)
- PFS as determined by the investigator
- ORR assessed by BICR according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
- ORR assessed by the investigator according to RECIST Version 1.1
- BOR, disease control rate (partial response [PR] + complete response [CR] + stable disease [SD]), and duration of response (only for subjects who have a response) assessed by BICR and by the investigator according to RECIST 1.1
- Type, frequency, and severity of adverse events (AEs) and serious AEs (SAEs), laboratory abnormalities, and other safety findings

Exploratory:

- PFS2 (from date of randomization until date of progression on the subsequent therapy or death due to any cause, whichever is earlier) as determined by the investigator
- QOL as measured by the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) C30, EORTC QLQ-BIL21, and EuroQOL five dimensions questionnaire (EQ-5D)
- PK parameters (C_{max}, C_{min}, and R_{acc})
- The prevalence of genomic alterations and their correlations with available clinicopathologic and demographic features in subjects with cholangiocarcinoma
- Genomic and proteomic assessments of tumor biopsies and cell-free DNA (blood) at baseline, during treatment, and at disease progression; and determination of the prognostic and/or predictive value of biomarkers to the clinical endpoints

Study Design: This is a multi-center, open label, randomized, controlled Phase 3 study to determine if treatment with infigratinib improves PFS assessed by BICR (primary objective) and OS (key secondary objective) compared to treatment with gemcitabine and cisplatin in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion/rearrangement. For the purposes of this protocol, "advanced/metastatic or inoperable" (as in the protocol title) is equivalent to "unresectable locally advanced or metastatic" (protocol-defined study population).

Subjects will be randomized in a 2:1 ratio to receive oral infigratinib administered once daily for the first 3 weeks (21 days) of a 28-day treatment cycle compared to a regimen of gemcitabine with cisplatin given on Days 1 and 8 of a 21-day cycle. Randomization will be stratified by locally advanced vs metastatic disease, geographic region (North America, Western Europe, Asia Pacific, and rest of the world), prior neoadjuvant/adjuvant treatment (yes/no), and received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no).

During the treatment period, subjects will be radiographically evaluated every 8 weeks ±7 days from the first dose of study drug, regardless of drug interruption, for tumor response (RECIST 1.1). When the decision is made to discontinue study drug, subjects will complete an End of Treatment (EOT) visit, no later than 8 days from the decision to discontinue study drug, and a Safety Follow-up visit no more than 30 days after last dose of study drug. If a subject discontinues study drug for reasons other than progressive disease (PD) confirmed by BICR, a

radiographic assessment should be conducted at the EOT visit, unless taken within the previous 4 weeks.

Subjects who discontinue study drug for radiographic PD confirmed by BICR will be followed approximately every 3 months (via telephone or office visit) for survival status and new anticancer therapy information (subsequent therapy and progression/PFS2) until End of Study (EOS), defined as the time when at least 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment. Subjects who discontinue study drug for reasons other than PD confirmed by BICR will continue to have radiographic assessments every 8 weeks ±7 days until radiographic PD confirmed by BICR. Thereafter, these subjects will be followed approximately every 3 months for survival status and use of anticancer therapy, as described above.

Sparse PK blood samples will be collected from all subjects in the infigratinib group at multiple time points, predose (C_{min} infigratinib) and 4 hours (±30 minutes) postdose (C_{max} infigratinib). Plasma concentrations of infigratinib and its metabolites (including BHS697 and CQM157) will be measured.

For a PK substudy, blood samples will be collected, at multiple time points (predose [C_{min} infigratinib], 4 hours [±30 minutes] postdose, and 24 hours postdose [±1 hour]) from the first 40 subjects who receive infigratinib. Plasma concentration of infigratinib and its active metabolites will be measured and PK parameters will be assessed.

Following radiographic PD confirmed by BICR, subjects randomized to the gemcitabine with cisplatin group may be eligible to cross over and receive infigratinib; these subjects will be followed for safety and OS.

Number of subjects (planned): Approximately 300 subjects with a likely or known activating FGFR2 fusion/rearrangement determined by a central laboratory or local laboratory are planned for study participation.

Diagnosis and criteria for inclusion and exclusion: To be eligible for the study, subjects must meet all of the following criteria:

1. Have histologically or cytologically confirmed unresectable locally advanced or metastatic cholangiocarcinoma. Subjects with gallbladder cancer or ampulla of Vater carcinoma are not eligible.

2. Have written documentation of local laboratory or central laboratory determination of a known or likely activating FGFR2 fusion/rearrangement from a sample collected before randomization (refer to Section 10.3.1 for the definition of a known or likely activating FGFR2 fusion/rearrangement). Note: All subjects enrolled based on local molecular test results must have sufficient tumor tissue for confirmation of FGFR2 fusion/rearrangement by the central laboratory, but this central confirmation is not required prior to enrollment in the study.
3. Have an archival tumor tissue sample available with sufficient tumor content for FGFR2 fusion/rearrangement molecular testing by the central laboratory. However, if an archival tumor tissue sample is not available or does not meet requirements for central testing, a newly obtained (before randomization) tumor biopsy may be submitted instead. If a prestudy written documentation of FGFR2 fusion/rearrangement in tumor tissue is available from the central laboratory, an additional tumor sample does not need to be submitted.
4. Have full recovery from the following permitted prior treatments (as applicable) such that the subject is reasonably expected to tolerate study treatment (gemcitabine/cisplatin or infigratinib) according to the investigator's assessment:

a. A non-curative operation (ie, R2 resection [with macroscopic residual disease] or palliative bypass surgery only)
b. Curative surgery with evidence of unresectable disease relapse requiring systemic chemotherapy
c. Adjuvant radiotherapy (with or without radio-sensitizing low-dose chemotherapy) for localized disease provided there has been clear evidence of disease progression before inclusion in this study
d. Adjuvant or neoadjuvant chemotherapy, provided recurrence occurred >6 months after the date of the last dose of adjuvant or neoadjuvant therapy and before randomization
e. Gemcitabine-based chemotherapy (specified in Appendix 5 [Section 17.5]) for advanced/unresectable or metastatic cholangiocarcinoma (≤1 cycle)
    i. Recovery from acute toxicities to the extent that would allow initiation of cisplatin-gemcitabine (absolute neutrophil count (ANC) ≥1,000/mm^3 (≥1.0 × 10^9/L); platelets ≥100,000/mm^3 (≥100× 10^9/L)
    ii. Baseline tumor assessment at least 7 days after the last dose of chemotherapy and before randomization
    iii. The window between the last dose of chemotherapy and the start of randomized study treatment must be ≥14 days and ≤5 weeks
f. Photodynamic treatment provided there is clear evidence of disease progression at the local site or at a new metastatic site

5. Are ≥18 years of age of either gender.
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
7. Have a life expectancy >3 months.
8. Are able to read and/or understand the details of the study and provide written evidence of informed consent as approved by Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
9. Are able to swallow and retain oral medication.
10. Are willing and able to comply with scheduled visits, treatment plan and laboratory tests.
11. If a woman of childbearing potential (WOCBP), must have a negative pregnancy test within 7 days of the first dose of study drug. A woman is not of childbearing potential if she has undergone surgical sterilization (total hysterectomy, or bilateral tubal ligation or bilateral oophorectomy at least 6 weeks before taking study drug) or if she is postmenopausal and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for at least 12 months, with an appropriate clinical profile, and there is no other cause of amenorrhea (eg, hormonal therapy, prior chemotherapy).

    WOCBP and males whose sexual partners are WOCBP must agree to use barrier contraception and a second form of highly effective contraception (Clinical Trials Facilitation Group 2014; see Appendix 3 [Section 17.3]) while receiving study drug and for 1 month following their last dose of infigratinib or 6 months following their last dose of gemcitabine/cisplatin (or according to local labeling and standard institutional practice). Alternatively, total abstinence is also considered a highly effective contraception method when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    Sexually active males must use a condom during intercourse while taking drug and for 1 month after the last dose of infigratinib or 6 months after their last dose of

gemcitabine/cisplatin (or according to local labeling and standard institutional practice) and should not father a child during this period. A condom is required to be used by vasectomized men and by men having intercourse with a male partner, to prevent delivery of the drug via seminal fluid.

To be eligible for the study, subjects must not meet any of the following criteria:

1. Have received treatment with any systemic anti-cancer therapy for unresectable locally advanced or metastatic cholangiocarcinoma, with the following exceptions:
   a. Prior neoadjuvant or adjuvant therapy is permitted if documented disease recurrence occurred ≥6 months after the last date of neoadjuvant or adjuvant therapy
   b. One cycle of gemcitabine-based chemotherapy (specified in Appendix 5 [Section 17.5]) for locally advanced or metastatic cholangiocarcinoma is permitted before randomization
2. Have history of a liver transplant.
3. Have previously or currently is receiving treatment with a mitogen-activated protein kinase (MEK) or selective FGFR inhibitor.
4. Have neurological symptoms related to underlying disease requiring increasing doses of corticosteroids. Note: Steroid use for management of central nervous system tumors is allowed but must be at a stable or decreasing dose of corticosteroids for at least 2 weeks preceding randomization.
5. Have a history of another primary malignancy within 3 years except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin or any other curatively treated or surveilled malignancy (eg, localized low-risk prostate cancer) that is not expected to require treatment for recurrence during the course of the study.
6. Have any other medical condition that would, in the investigator's judgment, prevent the subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
7. Have current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis, or diabetic retinopathy, confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.
8. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, vascular system, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification.
9. Have impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
10. Have current evidence of endocrine alterations of calcium/phosphate homeostasis, eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis, etc.
11. Are currently receiving or are planning to receive during participation in this study, treatment with agents that are known moderate or strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone. See Appendix 2 (Section 17.2) for details.

12. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits within 7 days prior to first dose of study drug.
13. Have insufficient bone marrow function:
    a. Absolute neutrophil count (ANC) <1,000/mm^3 (1.0×10^9/L)
    b. Platelets <100,000/mm^3 (<100× 10^9/L)
    c. Hemoglobin <8.5 g/dL; transfusion support is allowed if >1 week before randomization and hemoglobin remains stable
14. Have insufficient hepatic and renal function:
    a. Total bilirubin >1.5 × upper limit of normal (ULN) (for patients with documented Gilbert syndrome, direct bilirubin must be ≤1. 5 × ULN and enrollment requires approval by the medical monitor)
    b. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) >2.5 × ULN (AST and ALT >5 × ULN in the presence of liver involvement of cholangiocarcinoma)
    c. Calculated (using the Cockcroft-Gault formula [Cockcroft and Gault 1976]) or measured creatinine clearance of <45 mL/min (or value ≥45 mL/min that excludes administration of cisplatin per local label and institutional guidelines)
15. Have amylase or lipase >2.0 × ULN
16. Have elevated phosphorus or abnormal serum calcium, or calcium-phosphorus product ≥55 mg^2/dL^2 (refer to Section 9.3 for guidance on calculation):
    a. Inorganic phosphorus >1.1 × ULN
    b. Total corrected serum calcium >11 mg/dL or <8 mg/dL
17. Have clinically significant cardiac disease including any of the following:
    a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥2B) or uncontrolled hypertension (refer to the European Society of Cardiology and European Society of Hypertension guidelines [Williams et al 2018])
    b. Presence of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade ≥2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality
    c. Unstable angina pectoris or acute myocardial infarction ≤3 months prior to first dose of study drug
    d. QTcF >470 msec (males and females). Note: If the QTcF is >470 msec in the first electrocardiogram (ECG), a total of 3 ECGs separated by at least 5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤470 msec, the subject meets eligibility in this regard
    e. Known history of congenital long QT syndrome
18. Have had a recent (≤3 months prior to first dose of study drug) transient ischemic attack or stroke.
19. CTCAE (v5.0) Grade ≥2 hearing loss.
20. CTCAE (v5.0) Grade ≥2 neuropathy.

21. If female, is pregnant or nursing (lactating), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or blood laboratory test.
22. Have known microsatellite instability-high (MSI-H) disease and the decision is made by the treating investigator that an alternative, non-study therapy is warranted according to standard of care.
23. Have any known hypersensitivity to gemcitabine, cisplatin, calcium-lowering agents, infigratinib, or their excipients.
24. Have any contraindication to cisplatin or gemcitabine treatment according to local labeling or standard institutional practice.
25. Have taken any Chinese herbal medicine or Chinese patent medicine treatments with anticancer activity within 14 days of the first dose of study drug.
26. Have received a live vaccine within 30 days before the first dose of study drug or are planning to receive a live vaccine during participation in this study.

Investigational product, dosage and mode of administration: Subjects randomized to the infigratinib group will receive hard gelatin capsules for oral infigratinib 125 mg QD (administered as one 100-mg capsule and one 25-mg capsule) using a "3 weeks on, 1 week off" schedule for each 28-day treatment cycle (FMI IV formulation).

Reference therapy, dosage and mode of administration: Subjects randomized to the gemcitabine plus cisplatin group will receive intravenous infusions of gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on Days 1 and 8 of each 21-day treatment cycle according to each country's respective labeling and local institutional practices. It is recommended to have cisplatin infused over 1 hour in 1000 mL of 0.9% saline containing 20 mmol potassium chloride and 8 mmol magnesium sulfate, followed by 500 mL of 0.9% saline over an additional 30 minutes before initiation of the gemcitabine infusion. The cisplatin infusion should be performed with adequate hydration according to the institution's practice. After cisplatin administration, gemcitabine, diluted in 0.9% saline according to local labeling, will be infused over approximately 30 minutes.

Duration of treatment: Treatment will continue until radiographic PD confirmed by BICR, unacceptable toxicity, or other reason listed in Section 8.1.1.

If a subject in the gemcitabine and cisplatin group cannot tolerate cisplatin, they can remain on gemcitabine alone. However, if gemcitabine is discontinued due to toxicity then all study treatment must be discontinued. The subject will have an EOT visit and then continue on study for PFS, PFS2, and OS follow-up (even if the subject starts new anticancer treatment).

After radiographic PD confirmed by BICR, subjects randomized to gemcitabine with cisplatin may be eligible to cross over and receive infigratinib. Subjects who cross over to infigratinib will continue until unacceptable toxicity or other criterion listed in Section 8.1.1 has been met.

Criteria for evaluation:

Efficacy: Tumor response will be evaluated by BICR and by the investigator according RECIST Version 1.1 (Eisenhauer et al 2009). Subject management will be based upon investigator evaluations; subjects should remain on study drug until PD is confirmed by BICR.

Survival status and use of new anticancer medications will be followed approximately every 3 months once PD has been documented and confirmed by BICR. Survival status, use of anticancer therapy, and PFS2 will be followed until EOS.

Safety: Assessments will be performed at Screening and visits throughout the treatment period (Section 2): AEs and SAEs, clinical laboratory tests (blood and urine), vital signs, physical examinations, ECOG performance status, and electrocardiograms (ECGs), and ophthalmic assessments. AEs and SAEs will be assessed through 30 days post-treatment.

QOL: Subject QOL will be evaluated using the EQ-5D, which measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, anxiety, and general health; the EORTC QLQ-C30, a reliable and valid measure of QOL in subjects with cancer; and the EORTC QLQ-BIL21, a disease-specific module for subjects with cholangiocarcinoma and gallbladder cancer.

PK (infigratinib group only): All subjects in the infigratinib group will have PK blood samples collected on Day 21 of Cycles 1 through 4 at 0 (predose) and 4 hours (±30 minutes) postdose. The PK parameters C_{max}, C_{min}, and $R_{acc,}$ will be calculated.

In addition, a PK substudy will be conducted on the first 40 subjects enrolled who receive infigratinib. These subjects will have PK blood samples collected at the following time points in Cycle 1: Day 1 (0 [predose] and 4 hours [±30 minutes] postdose), Day 2 (24 hours [±1 hour] after the Day 1 dose prior to Day 2 dosing), Day 21 (0 [predose] and 4 hours [±30 min] postdose), Day 22 (24 hours [±1 hour] after the Day 21 dose), and the same as all other subjects in the infigratinib group: Day 21 of Cycles 2 through 4 at 0 (predose) and 4 hours (±30 minutes) postdose.

For any subject in the infigratinib group who permanently discontinues study drug for any reason, attempts should be made to collect a PK blood sample from the subject at the time of discontinuation, if the sample can be collected within 24 hours of last dose.

Blood samples will be collected to measure plasma concentrations of infigratinib and its metabolites (eg, BHS697 and CQM157). On days of PK sampling, subjects should bring their study drug with them to the clinic and take it after the predose PK sample is taken.

Biomarkers: Archival or newly obtained tumor samples will be collected to evaluate biomarkers related to cholangiocarcinoma biology and their potential correlation to efficacy, disease progression, and resistance to study medications using genetic and protein analysis of the tumor. Blood samples will also be collected for assessment of cell-free DNA.

Statistical methods:

Sample Size: Approximately 300 subjects with FGFR2 fusion/rearrangement determined by a central laboratory or local laboratory will be randomized in the study (2:1 randomization, with 200 in the infigratinib group and 100 in gemcitabine with cisplatin group) and stratified by unresectable locally advanced vs metastatic disease, geographic region (North America, Western Europe, Asia Pacific, and rest of the world), prior neoadjuvant/adjuvant treatment (yes/no), and received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no).

The primary endpoint is PFS assessed by BICR. Assuming a PFS hazard ratio (HR) of 0.67 (median PFS 11.9 vs 8 months) (Valle et al 2010) comparing infigratinib to gemcitabine with cisplatin, with 228 PFS events required, the study will provide approximately 80% power to determine if infigratinib improves PFS assessed by BICR compared to treatment with gemcitabine and cisplatin at a 2-sided significance level of 0.05. Assuming the test on PFS is significant, with 224 deaths observed, the study will provide 66% power to demonstrate infigratinib improves OS compared to treatment with gemcitabine and cisplatin assuming an OS HR of 0.7 (median OS 16.7 vs 11.7 months) (Valle et al 2010).

The study employs a group sequential design with one interim analysis for futility on PFS, which will be conducted when approximately 50% of the PFS events (114) are observed. The primary analysis for PFS will be conducted after approximately 228 PFS events have been

observed. A fixed 2-sided significance level of 0.0001 will be spent at the interim analysis for PFS. A Lan-DeMets alpha spending function approximating O'Brien Fleming boundaries will be used for the interim non-binding futility and final boundary.

One interim analysis and one primary analysis for OS are planned. The interim analysis for OS will be conducted at the PFS primary analysis, and the primary analysis for OS will be conducted after approximately 224 deaths have been observed. OS will be tested only if PFS is found to be significant. The Lan-DeMets spending function approximating the O'Brien-Fleming spending function will be used to calculate the significance boundaries.

With 42-month uniform enrollment, the study is projected to reach the planned number of PFS events assessed by BICR (228) in approximately 54 months from randomization of the first subject. The OS event goal of 224 deaths is projected to be reached approximately 66 months from randomization of the first subject. The required sample size is estimated to be a total of 300 subjects, considering that approximately 10% of subjects will drop out per year before a PFS or OS event.

Efficacy Analyses: The efficacy analyses will be conducted on the ITT population unless otherwise specified. This population will include all subjects who are randomized. Subjects will be analyzed according to the treatment group to which they are randomized. The stratified log-rank test (using the randomization stratification factors) will be used to compare the treatment arms with respect to PFS assessed by BICR and OS. The HR and the corresponding 2-sided 95% confidence interval (CI) will be derived from a stratified Cox proportional hazards regression model using randomization stratification factors for PFS assessed by BICR and OS. The Kaplan-Meier (K-M) medians (if estimable) will be derived, along with their 2-sided 95% CIs. Sensitivity analyses will be conducted on OS to address the impact of subjects' crossover.

The primary endpoint, PFS assessed by BICR, will be tested first at 2-sided significance level of 0.05. The key secondary endpoint, OS, will only be tested if the test on PFS assessed by BICR is significant.

The 2-sided 95% CI will be calculated for the difference in ORR between the 2 treatment groups based on the Wilson method for subjects in the ITT population. PFS based on investigator assessment will be analyzed using a stratified log-rank test and corresponding 2-sided 95% CI for the HR from the stratified Cox proportional hazards regression model. Response duration will be summarized by the K-M method, and descriptive summaries will be provided for BOR and disease control rate (PR+CR+SD). PFS2 will be analyzed using the same approaches as for investigator-assessed PFS.

Safety Analyses: All reported AEs will be assigned a system organ class and preferred term, according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. All AEs (including serious and drug-related) of subjects who receive at least one dose of study drug will be tabulated from first dose through 30 days after last dose of study drug.

Interim Analysis: One formal interim analysis of PFS based on BICR will be performed when approximately 114 PFS events have occurred across both treatment arms in the ITT population. One interim analysis for OS will be conducted at the time of the PFS primary analysis.

The study may be stopped due to futility at the interim PFS analysis if the futility boundary for testing PFS is crossed. The futility stopping boundary is non-binding to allow for additional considerations. Though efficacy boundaries are specified for PFS assessed by BICR at the time of the interim PFS analysis, the trial will not stop for efficacy at the interim analysis for PFS even if the efficacy boundary is crossed for PFS.

Other Information: An independent Data Monitoring Committee (DMC) will review safety and efficacy data at the interim analyses. In addition, the DMC will periodically review safety data at regularly scheduled meetings, according to a prespecified DMC charter.

Full details of the planned statistical analyses will be included in the Statistical Analysis Plan.

2 SCHEDULE OF ASSESSMENTS

Schedules of assessments to be performed during the study are presented in Table 2 (infigratinib group), Table 4 (gemcitabine plus cisplatin group), and Table 5 (subjects in the gemcitabine plus cisplatin group who cross over to infigratinib). Table 3 outlines pharmacokinetics (PK) sampling times for subjects in the PK substudy, which will be composed of the first 40 subjects enrolled in the infigratinib group .

All data obtained from these assessments must be supported in the subject's source documentation.

Baseline/screening assessments must be conducted within 28 days before randomization. **Note:** for subjects who receive up to 1 cycle of gemcitabine-based chemotherapy before randomization, the baseline imaging assessment must be conducted ≥7 days after the last dose of chemotherapy and before randomization.

In the event that subjects have a baseline/screening laboratory assessment that excludes them from the study, the assessment can be repeated. Baseline/screening assessments that are conducted within 3 days prior to first treatment can be used to satisfy the Day 1 requirement. Every effort must be made to follow the schedule outlined.

Whenever feasible vaccinations should be administered at least 30 days prior to randomization. Live vaccines are prohibited within 30 days before the first dose of study drug, for the duration of study participation, and for a period of time (approximately 3-6 months) after the last dose of chemotherapy according to local guidelines (see also Section 7.7).

Unless otherwise indicated, there is a ±3-day window on assessments. For post-baseline imaging and ophthalmic assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted). The EOT visit is to be conducted no later than 8 days from the decision to discontinue study drug. In the PK substudy, there are no visit windows for the trough PK sampling days (Cycle 1 Day 2 and Cycle 1 Day 22).

Subjects without central confirmation of FGFR2 fusion/rearrangement will be able to continue study drug at the investigator's discretion; these subjects will follow the same study schedules as previously described.

Each subject will be tested for microsatellite instability (MSI) status as part of central testing for FGFR2 fusion/rearrangement. Subjects may randomize to the study prior to MSI results being available. If the subject is determined to be MSI-H prerandomization, then the investigator should decide if the subject is an appropriate candidate. If the subject is determined to be MSI-H postrandomization, the subject may continue on study treatment, but this requires joint decision by the subject and investigator and documentation of subject consent to continue on study treatment.

Table 2: Schedule of Assessments: Subjects in the Infigratinib Group

	Molecular Pre screening [a]	Screening [a]	Visits during Treatment Period (28-day Treatment Cycles: 3 Weeks on, 1 Week off)							EOT	30-day Safety Follow-up	Survival Follow-up Every 3 mo After Disease Progression [c]
			Wk1 D1	Wk2 D1	Wk3 D1	Wk3 D7			Each Additional Cycle			
Time of Study [b]		-28 to -1	Cycle 1				Cycles 2-4		Cycle 5+	No Later than 8d from Decision to DC Study Drug		
			D1	D8	D15	D21	D1	D21	D1			
Prescreening IC if FGFR2 data not available	X											
Prescreening molecular testing if FGFR2 data not available	X											
FGFR2 fusion/rearrangement documentation and confirmation of tumor availability for central testing [d]		X										
Collection of archival or a newly obtained tumor sample AND pathology report, if archival paraffin blocks/slides and pathology report not available	X	X [e]										
Main Study IC		X										
Demography		X										
I/E criteria		X										
ECOG Performance Status		X	X				X		X	X	X	
Relevant medical history/current medical conditions		X										
Diagnosis, primary location, and extent of cancer		X										
Prior anticancer therapy		X										
Height		X										
Weight [f]		X	X				X		X	X		
Randomization (within 5 days before Cycle 1 Day 1 [C1D1])		X										

	Molecular Pre screening [a]	Screening [a]	Visits during Treatment Period (28-day Treatment Cycles: 3 Weeks on, 1 Week off)							EOT	30-day Safety Follow-up	Survival Follow-up
			Wk1 D1	Wk2 D1	Wk3 D1	Wk3 D7			Each Additional Cycle			
Time of Study [b]		-28 to -1	Cycle 1				Cycles 2-4		Cycle 5+	No Later than 8d from Decision to DC Study Drug		Every 3 mo After Disease Progression [c]
			D1	D8	D15	D21	D1	D21	D1			
Infigratinib Dose Administration			Daily dosing using a "3 weeks on, 1 week off" schedule for each 28-day treatment cycle; C1D1 and C1-4 D21[o] doses are administered in the clinic.									
Adverse Events	Continuous [g]											
Prior/concomitant medications		Continuous										
Pregnancy test [f]		X	X				X		X	X		
Vital signs [f]		X	X	X	X	X	X		X	X		
Hematology [f]		X	X		X		X		X	X		
Chemistry [f]		X	X	X	X	X	X		X	X		
12-lead ECG [h]		X	X				X [h]			X		
Coagulation		X	If clinically indicated									
Urinalysis (micro- and macroscopic)		X	If clinically indicated									
Physical examination		X	Symptom-directed exams, as needed							X		
Ophthalmic assessment (performed by an ophthalmologist)		X					C2D1, C4D1, and every 3 months after [i]			X [i]		
CT/MRI scans of the chest, abdomen, and pelvis (also brain if clinically indicated)		X [j]	Tumor response will be assessed at Wk9D1 and every 8 wk (±1wk) thereafter until PD confirmed by BICR, regardless of drug interruption (RECIST 1.1). After PD is confirmed by BICR, tumor assessments will be completed only according to investigator assessment (no longer BICR-assessed). [k]									
EQ-5D, EORTC QLQ-C30, EORTC QLQ-BIL21 [l]			QOL assessments are every 4 weeks through Wk17D1 i.e, Wk1D1, Wk5D1, Wk9D1, Wk13D1, Wk17D1, and every 8 wk (±1wk) from last assessment, regardless of drug interruption							X		
Blood sample for assessment of cell-free tumor DNA (all samples are predose)			X[m]	Every 8 wk (±1wk) coinciding with CT/MRI scans, regardless of drug interruption [m]						X (if not done within 28 d prior)		
Blood sample for PK assessment (all subjects receiving infigratinib) [n]						X (0 and 4		X (0 and 4		X[n]		

	Molecular Pre screening [a]	Screening [a]	Visits during Treatment Period (28-day Treatment Cycles: 3 Weeks on, 1 Week off)							EOT	30-day Safety Follow-up	Survival Follow-up
			Wk1 D1	Wk2 D1	Wk3 D1	Wk3 D7			Each Additional Cycle			
Time of Study [b]		-28 to -1	Cycle 1				Cycles 2-4		Cycle 5+	No Later than 8d from Decision to DC Study Drug		Every 3 mo After Disease Progression [c]
			D1	D8	D15	D21	D1	D21	D1			
						hr postdose)		hr postdose)				
Survival follow-up												X
Anticancer therapies since discontinuation of study drug											X	X
Newly obtained tumor sample (if medically feasible)			X (upon disease progression)-optional									

Abbreviations: AE, adverse event; BICR, blinded independent central review; CT, computed tomography; d, day; DC, discontinue; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; EQ-5D, EuroQOL five dimensions questionnaire; FGFR2, fibroblast growth factor receptor 2; IC, informed consent; I/E, inclusion/exclusion; MRI, magnetic resonance imaging; NaF, sodium fluoride; OCT, optical coherence tomography; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PFS2, PFS on subsequent therapy; PK, pharmacokinetic; QLQ, quality of life questionnaire; RECIST, Response Evaluation Criteria in Solid Tumors;TC99, technetium-99.

[a] After prescreening ICF, molecular prescreening assessments can be done any time prior to the initiation of the screening. All baseline/screening assessments must be performed within 28 days before randomization. For subjects who receive up to 1 cycle of gemcitabine-based chemotherapy before randomization, the baseline imaging assessment must be conducted ≥7 days after the last dose of chemotherapy and before randomization. Baseline/screening assessments that are conducted within 3 days prior to first treatment can be used to satisfy the Day 1 requirement. Every effort must be made to follow the schedule outlined.

[b] Unless otherwise indicated, there is a ±3-day window on assessments. For post-baseline imaging and ophthalmic assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted). The EOT visit is to be conducted no later than 8 days from the decision to discontinue study drug.

[c] Once radiographic PD is confirmed by BICR and documented, survival status, use of anticancer therapy (names and dates of therapies, response, and reason for discontinuation), and date of subsequent progression (PFS2) will be followed approximately every 3 months (via telephone or office visit) until the End of Study, defined as the time when at least 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment.

[d] Central laboratory testing for FGFR2 fusion/rearrangement will include microsatellite instability status.

[e] If written documentation of FGFR2 fusion/rearrangement is determined by a local laboratory, archival or fresh biopsy tumor tissue sample must be submitted to the central laboratory within approximately 14 days of start of study treatment for the confirmation of FGFR2 fusion/rearrangement. Refer to the Laboratory Manual for the sample requirements and processing instructions for central laboratory testing of FGFR2 fusion/rearrangement.

[f] To be conducted within 3 days before the first dose of study drug is administered; all subsequent assessments may be conducted at any time relative to dosing (pre- or postdose), unless specified otherwise. If a subject is not dosed at a visit where dosing is scheduled, then the procedures specified for that visit must be completed/repeated on the actual dosing day.

[g] See Section 10.5.1.3 for details on the collection and recording of adverse events (including serious adverse events).

[h] For each subject, 12-lead ECGs are to be performed at the Screening visit; on Day 1 (predose) of Cycle 1, Day 1 of Cycle 2; at the EOT visit, and otherwise as clinically indicated.

[i] Ophthalmic assessment (performed by an ophthalmologist) will be done on C2D1, C4D1, and every 3 months after that. Ophthalmic assessment includes visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, intraocular pressure, retinal OCT, and dilated fundoscopy. Additional examination methods such as specular microscopy and corneal pachymetry will be done as clinically indicated. Retinal OCT scan images will be collected centrally for potential review. Refer to the Study Manual for details regarding image collection and transfer or shipment. Ophthalmic assessment will be conducted at EOT visit unless performed within previous 4 weeks.

[j] For subjects who receive up to 1 cycle of gemcitabine-based chemotherapy before randomization, the baseline imaging assessment must be conducted ≥7 days after the last dose of chemotherapy and before randomization. For subjects with skeletal lesions suspected at screening, whole-body bone imaging should be obtained either with a TC99 bone scan or alternatively a NaF CT/ MRI PET scan, with local CT of any identified lesions. Of note, the CT or MRI portion of the scan should only be substituted for the required chest, abdomen, and pelvic CT scans if the CT or MRI is of diagnostic quality and meets all requirements as described in the study imaging guide (ie, oral and IV contrast, slice thickness, and anatomic coverage). Postbaseline, if skeletal lesions are identified at screening, which are not visible on the chest, abdomen or pelvis CT/MRI scan, bone imaging with either a TC99 bone scan or NaF CT/MRI PET is required at all postbaseline imaging timepoints (every 8 weeks). In all cases that postbaseline bone imaging is required, the same modality that was used at screening should be used for all postbaseline imaging when possible.

[k] During the treatment period, subjects will be evaluated every 8 weeks from the first dose of study drug, regardless of drug interruption. For postbaseline imaging and ophthalmic assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted). If a subject discontinues study drug for reasons other than PD confirmed by BICR, a radiographic assessment should be conducted at the EOT visit, unless taken within the previous 4 weeks. Subjects who discontinue study drug for reasons other than PD confirmed by BICR will continue to have radiographic assessments every 8 weeks ±7 days until radiographic PD confirmed by BICR (even if subjects start new anticancer treatment). After PD is confirmed by BICR, tumor assessments will be completed only according to investigator assessment (no longer BICR-assessed).

[l] Quality of life assessments should be conducted prior to all other study procedures and in order of EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BIL21. Assessments do not need to be administered at the EOT visit if they were completed within the previous 7 days at a regularly scheduled visit.

[m] Blood for cell-free DNA should be collected on Day 1 of Cycle 1 (predose) and then every 8 wk (±1wk) at the same visit as CT/MRI scans. For subjects who discontinue therapy without radiographic PD confirmed by BICR, a blood sample for cell-free DNA should be taken once progression is confirmed by BICR and/or investigator.

[n] For all subjects in the infigratinib group, blood samples will be collected on Day 21 of Cycles 1 through 4 at 0 (predose) and 4 hours (±30 minutes) postdose. In addition, for any subject in the infigratinib group who permanently discontinues study drug for any reason, attempts should be made to collect a PK blood sample from the subject at the time of discontinuation, if the sample can be collected within 24 hours of last dose.
NOTE: On the days of PK dosing, subjects should not take their study drug dose at home; subjects should take their study drug with them to the study center where dosing of infigratinib will be supervised and administration time recorded.

Table 3: Schedule of Assessments: PK Sampling in a Substudy of 40 Subjects in the Infigratinib Group

		Visits during Treatment Period (28-day Treatment Cycles: 3 Weeks on, 1 Week off)							EOT
		Wk1 D1	Wk1 D2	Wk3 D7	Wk4 D1	Wk7 D7	Wk11 D7	Wk15 D7	
	Study Day:	1	2	21	22	49	77	105	
Time of Study		Cycle 1				Cycle 2	Cycle 3	Cycle 4	No Later than 8d from Decision to DC Study Drug
		D1	D2	D21	D22	D21	D21	D21	
Blood sample for PK assessment [a]		X (0 and 4 hr postdose)	X (24 hr post Day 1 dose)	X (0 and 4 hr postdose)	X (24 hr post Day 21 dose)	X (0 and 4 hr postdose)	X (0 and 4 hr postdose)	X (0 and 4 hr postdose)	X[b]

Abbreviations: AE, adverse event; d, day; DC, discontinue; EOT, end of treatment; PK, pharmacokinetic.

[a] For the first 40 subjects in the infigratinib group, blood samples will be collected at the following time points for PK analysis for Cycle 1: Cycle 1: Day 1 (0 [predose] and 4 hours [±30 minutes] postdose), Day 2 (24 hours [±1 hour] after the Day 1 dose prior to Day 2 dosing), Day 21 (0 [predose] and 4 hours [±30 min] postdose), and Day 22 (24 hours [±1 hour] after the Day 21 dose). For Cycles 2 through 4, blood samples will be collected on Day 21 (0 [predose] and 4 hr [±30 min] postdose) of each respective cycle.

[b] For any subject in the infigratinib group who permanently discontinues study drug for any reason, attempts should be made to collect a PK blood sample from the subject at the time of discontinuation, if the sample can be collected within 24 hours of last dose.

NOTE: There are no visit windows for the trough PK sampling days (Cycle 1 Day 2 and Cycle 1 Day 22). On the days of PK sampling, subjects should not take their study drug dose at home; subjects should take their study drug with them to the study center where dosing of infigratinib will be supervised and administration time recorded.

Table 4: Schedule of Assessments: Subjects in the Gemcitabine plus Cisplatin Group

	Molecular Pre screening [a]	Screening [a]	Visits during Treatment Period (21-day Treatment Cycles: Infusions on Day 1 and Day 8 of each Cycle)				EOT	30-day Safety Follow-up	Survival Follow-up
			Wk1 D1	Wk2 D1	Each Additional Cycle				
Time of Study [b]		-28 to -1	Cycle 1		Cycle 2-8+		No Later than 8d from Decision to DC Study Drug		Every 3 mo After Disease Progression [c]
			D1	D8	D1	D8			
Prescreening IC if FGFR2 data not available	X								
Prescreening molecular testing if FGFR2 data not available	X								
FGFR2 fusion/rearrangement documentation and confirmation of tumor availability for central testing [d]		X							
Collection of archival or a newly obtained tumor sample AND pathology report, if archival paraffin blocks/slides and pathology report not available	X	X [e]							
Main Study IC		X							
Demography		X							
I/E criteria		X							
ECOG Performance Status		X	X		X		X	X	
Relevant medical history/current medical conditions		X							
Diagnosis, primary location, and extent of cancer		X							
Prior anticancer therapy		X							
Height		X							
Weight [h]		X	X		X		X		
Randomization (within 5 days before Cycle 1 Day 1)		X							
Gemcitabine/ Cisplatin Dose Administration [f]			X	X	X	X			
Adverse Events	Continuous [g]								
Prior/concomitant medications		Continuous							
Pregnancy test [h]		X	X		X		X		
Vital signs [h]		X	X	X	X	X	X		
Hematology [h]		X	X	X	X	X	X		
Chemistry [h]		X	X	X	X	X	X		
12-lead ECG [h]		X	X		X		X		
Coagulation		X	If clinically indicated						
Urinalysis (micro- and macroscopic)		X	If clinically indicated						
Physical examination		X	Symptom-directed exams, as needed				X		

	Molecular Pre screening [a]	Screening [a]	Visits during Treatment Period (21-day Treatment Cycles: Infusions on Day 1 and Day 8 of each Cycle)				EOT	30-day Safety Follow-up	Survival Follow-up
			Wk1 D1	Wk2 D1	Each Additional Cycle				
Time of Study [b]		-28 to -1	Cycle 1		Cycle 2-8+		No Later than 8d from Decision to DC Study Drug		Every 3 mo After Disease Progression [c]
			D1	D8	D1	D8			
Ophthalmic assessment (performed by an ophthalmologist) [i]		X			C2D8, C5D1, and every 3 months after [j]		X [j]		
CT/MRI scans of the chest, abdomen, and pelvis (also brain if clinically indicated)		X [k]	Tumor response will be assessed at Wk9D1 and every 8 wk (±1wk) thereafter until PD confirmed by BICR, regardless of drug interruption (RECIST 1.1). After PD is confirmed by BICR, tumor assessments will be completed only according to investigator assessment (no longer BICR-assessed). [l]						
EQ-5D, EORTC QLQ-C30, EORTC QLQ-BIL21 [m]			QOL assessments are every 4 weeks through Wk17D1 i.e, Wk1D1, Wk5D1, Wk9D1, Wk13D1, Wk17D1, and every 8 wk (±1wk) from last assessment, regardless of drug interruption				X		
Blood sample for assessment of cell-free tumor DNA (all samples are predose)			X [n]	Every 8 wk (±1wk) coinciding with CT/MRI scans, regardless of drug interruption [n]			X (if not done within 28 d prior)		
Survival follow-up									X
Anticancer therapies since discontinuation of study drug								X	X
Newly obtained tumor sample (if medically feasible)			X (upon disease progression)-optional						

Abbreviations: AE, adverse event; BICR, blinded independent central review; CT, computed tomography; d, day; DC, discontinue; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; EQ-5D, EuroQOL five dimensions questionnaire; FGFR2, fibroblast growth factor receptor 2; IC, informed consent; I/E, inclusion/exclusion; MRI, magnetic resonance imaging; NaF, sodium fluoride; OCT, optical coherence tomography; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PFS2, PFS on subsequent therapy; PK, pharmacokinetic; QLQ, quality of life questionnaire; RECIST, Response Evaluation Criteria in Solid Tumors;TC99, technetium-99.

[a] After prescreening ICF, molecular prescreening assessments can be done any time prior to the initiation of the screening. All baseline/screening assessments must be performed within 28 days before randomization. For subjects who receive up to 1 cycle of gemcitabine-based chemotherapy before randomization, the baseline imaging assessment must be conducted ≥7 days after the last dose of chemotherapy and before randomization. Baseline/screening assessments that are conducted within 3 days prior to first treatment can be used to satisfy the Day 1 requirement. Every effort must be made to follow the schedule outlined.

[b] Unless otherwise indicated, there is a ±3-day window on assessments. For post-baseline imaging and ophthalmic assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted). The EOT visit is to be conducted no later than 8 days from the decision to discontinue study drug.

[c] Once radiographic PD is confirmed by BICR and documented, survival status, use of anticancer therapy (names and dates of therapies, response, and reason for discontinuation) and date of subsequent progression (PFS2) will be followed approximately every 3 months (via telephone or office visit) until the End of Study, defined as the time when at least 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment.

[d] Central laboratory testing for FGFR2 fusion/rearrangement will include microsatellite instability status.

[e] If written documentation of FGFR2 fusion/rearrangement is determined by a local laboratory, archival or fresh biopsy tumor tissue sample must be submitted to the central laboratory within approximately 14 days of start of study treatment for the confirmation of FGFR2 fusion/rearrangement. Refer to the Laboratory Manual for the sample requirements and processing instructions for central laboratory testing of FGFR2 fusion/rearrangement.

[f] Subjects will receive gemcitabine plus cisplatin on Day 1 and Day 8 of each 21-day treatment cycle until radiographic PD confirmed by BICR; unacceptable toxicity; or other reason listed in Section 8.1.1. Following radiographic PD confirmed by BICR, subjects randomized to the gemcitabine with cisplatin group may be eligible to cross over and receive infigratinib (see Section 7.1). If one or more toxicities result in delay of cycle start, the cycle will be considered to start on the first day when any chemotherapy is administered. Subjects who cannot start a cycle within 21 days of the scheduled Day 1 (ie, within 42 days of the previous cycle Day 1) must permanently discontinue all chemotherapy unless approved by the sponsor medical monitor. If Day 8 dosing can't be given by Day 15 of a 21-day cycle, the subject should skip the Day 8 dose and dosing will resume on Day 1 of the next scheduled cycle.

[g] See Section 10.5.1.3 for details on the collection and recording of adverse events (including serious adverse events).

[h] To be conducted within 3 days before the first study treatment is administered; all subsequent assessments may be conducted at any time relative to treatment (pre- or post-treatment), unless specified otherwise. For each subject, 12-lead ECGs are to be performed at the Screening visit; on Day 1 (predose) of Cycle 1, Day 1 of Cycle 2, at the EOT visit, and otherwise as clinically indicated.

[i] If a subject is not dosed at a visit where dosing is scheduled, then the procedures specified for that visit must be completed/repeated on the actual dosing day, with the exception of ophthalmic assessment (performed by an ophthalmologist).

[j] Ophthalmic assessment (performed by an ophthalmologist) will be done C2D8, C5D1, and every 3 months after that. Ophthalmic assessment includes visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, intraocular pressure, retinal OCT, and dilated fundoscopy. Additional examination methods such as specular microscopy and corneal pachymetry will be done as clinically indicated. Retinal OCT scan images will be collected centrally for potential review. Refer to the Study Manual for details regarding image collection and transfer or shipment. Ophthalmic assessment will be conducted at EOT visit unless performed within previous 4 weeks.

[k] For subjects who receive up to 1 cycle of gemcitabine-based chemotherapy before randomization, the baseline imaging assessment must be conducted ≥7 days after the last dose of chemotherapy and before randomization. For subjects with skeletal lesions suspected at screening, whole-body bone imaging should be obtained either with a TC99 bone scan or alternatively a NaF CT/ MRI PET scan, with local CT of any identified lesions. Of note, the CT or MRI portion of the scan should only be substituted for the required chest, abdomen, and pelvic CT scans if the CT or MRI is of diagnostic quality and meets all requirements as described in the study imaging guide (ie, oral and IV contrast, slice thickness, and anatomic coverage). Postbaseline, if skeletal lesions are identified at screening, which are not visible on the chest, abdomen or pelvis CT/MRI scan, bone imaging with either a TC99 bone scan or NaF CT/MRI PET is required at all postbaseline imaging timepoints (every 8 weeks). In all cases that postbaseline bone imaging is required, the same modality that was used at screening should be used for all postbaseline imaging when possible.

[l] During the treatment period, subjects will be evaluated every 8 weeks from the first dose of study drug, regardless of drug interruption. For post-baseline imaging andophthalmic assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted). If a subject discontinues study drug for reasons other than PD confirmed by BICR, a radiographic assessment should be conducted at the EOT visit, unless taken within the previous 4 weeks. Subjects who discontinue study drug for reasons other than PD confirmed by BICR will continue to have radiographic assessments every 8 weeks ±7 days until radiographic PD confirmed by BICR (even if subjects start new anticancer treatment). After PD is confirmed by BICR, tumor assessments will be completed only according to investigator assessment (no longer BICR-assessed).

[m] Quality of life assessments should be conducted prior to all other study procedures and in order of EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BIL21. Assessments do not need to be administered at the EOT visit if they were completed within the previous 7 days at a regularly scheduled visit.

[n] Blood for cell-free DNA should be collected Day 1 of Cycle 1 (predose) and then every 8 wk (±1wk) at the same visit as CT/MRI scans. For subjects who discontinue therapy without radiographic PD confirmed by BICR, a blood sample for cell-free DNA should be taken once progression is confirmed by BICR and/or investigator.

Table 5: Schedule of Assessments: Subjects in the Gemcitabine plus Cisplatin Group who Cross Over to Infigratinib

Time of Study [a]	Visits during Treatment Period (To be Followed Once a Subject in the Gemcitabine plus Cisplatin Group has PD Confirmed by BICR and Crosses Over to Infigratinib) [b]								EOT No Later than 8 d from Decision to DC Study Drug	30-day Safety Follow-up	Survival Follow-up Every 3 mo [c]
	Wk1 D1	Wk2 D1	Wk3 D1	Wk4 D1	Wk5 D1	Wk9 D1	Wk13 D1	Each Additional Cycle			
	Cycle 1				Cycle 2	Cycle 3	Cycle 4	Cycle 5+			
	D1	D8	D15	D22	D1	D1	D1	D1			
I/E criteria	X [d]										
ECOG Performance Status	X				X	X	X	X	X	X	
Infigratinib (*Crossover*)	Daily dosing using a "3 weeks on, 1 week off" schedule for each 28-day treatment cycle										
Adverse Events	Continuous										
Prior/ concomitant medications	Continuous										
Pregnancy test [e]	X				X	X	X	X	X		
Vital signs [e]	X	X	X	X	X	X	X	X	X		
Hematology [e]	X		X		X	X	X	X	X		
Chemistry [e]	X	X	X	X	X	X	X	X	X		
12-lead ECG [e, f]	X				X				X		
Coagulation	If clinically indicated										
Urinalysis (micro- and macroscopic)	If clinically indicated										
Physical examination	Symptom-directed exams, as needed								X		
Ophthalmic assessment (performed by an ophthalmologist) [e]	C2D1, C4D1, and every 3 months after [g]								X [g]		
CT/MRI scans of the chest, abdomen, and pelvis (also brain if clinically indicated)	Tumor response will be assessed at Wk9D1 and every 8 wk (±1wk) thereafter until PD confirmed by BICR, regardless of drug interruption (RECIST 1.1). After PD is confirmed by BICR, tumor assessments will be completed only according to investigator assessment (no longer BICR-assessed).[h]										
Blood sample for assessment of cell-free tumor DNA (all samples are predose)	X	Every 8 wk (±1wk) coinciding with CT/MRI scans, regardless of drug interruption [i]							X (if not done within 28 d prior)		
Survival follow-up											X

Abbreviations: d, day; DC, discontinue; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; FGFR2, fibroblast growth factor receptor 2; I/E, inclusion/exclusion; MRI, magnetic resonance imaging; NaF, sodium

fluoride; OCT, optical coherence tomography; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; QLQ, quality of life questionnaire; RECIST, Response Evaluation Criteria in Solid Tumors; TC99, technetium-99.

[a] For all visits, there is a ±3-day window on assessments, if not explicitly specified otherwise. The EOT visit is to be conducted no later than 8 days from the decision to discontinue study drug.

[b] Subjects randomized to the gemcitabine with cisplatin group who cross over to receive infigratinib must complete their 30-day Safety Follow-up visit for gemcitabine with cisplatin before receiving any infigratinib.

[c] Survival status will be followed approximately every 3 months (via telephone or office visit) until the End of Study, defined as the time when at least 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment.

[d] Before subjects in the gemcitabine/cisplatin cross over and receive any infigratinib, the following exclusion criteria must be rechecked: Exclusion Criteria 4, 7-10, 13, 14, 16-18. Assessments performed within the past 30 days may be used to check these criteria. If the subject is receiving ondansetron, its use must be discontinued with a washout period of at least 24 hours before receiving any infigratinib.

[e] If a subject is not dosed at a visit where dosing is scheduled, then the procedures specified for that visit must be completed/repeated on the actual dosing day, with the exception of ophthalmic assessment (performed by an ophthalmologist).

[f] For each subject, 12-lead ECGs are to be performed on Days 1 (predose) and 15 of Cycle 1; on Day 1 of Cycle 2; at the EOT visit, and otherwise as clinically indicated.

[g] Ophthalmic assessment (performed by an ophthalmologist) will be done on C2D1, C4D1, and every 3 months after that. Ophthalmic assessment includes visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, intraocular pressure, retinal OCT, and dilated fundoscopy. Additional examination methods such as specular microscopy and corneal pachymetry will be done as clinically indicated. Retinal OCT scan images will be collected centrally for potential review. Refer to the Study Manual for details regarding image collection and transfer or shipment. Ophthalmic assessment will be conducted at EOT visit unless performed within previous 4 weeks.

[h] For subjects with existing or suspected new skeletal lesions, whole-body bone imaging should be obtained either with a TC99 bone scan or alternatively a NaF CT/ MRI PET scan, with local CT of any identified lesions. Of note, the CT or MRI portion of the scan should only be substituted for the required chest, abdomen, and pelvic CT scans if the CT or MRI is of diagnostic quality and meets all requirements as described in the study imaging guide (ie, oral and IV contrast, slice thickness, and anatomic coverage). Postbaseline, if skeletal lesions are identified at screening, which are not visible on the chest, abdomen or pelvis CT/MRI scan, bone imaging with either a TC99 bone scan or NaF CT/MRI PET is required at all postbaseline imaging timepoints (every 8 weeks). In all cases that postbaseline bone imaging is required, the same modality that was used at screening should be used for all postbaseline imaging when possible.

[i] Blood for cell-free DNA should be collected at Day 1 of Cycle 1 (predose) of starting infigratinib treatment and then every 8 wk (±1wk) from last assessment, regardless of drug interruption. For subjects who discontinue therapy without radiographic PD confirmed by BICR, a blood sample for cell-free DNA should be taken once progression is confirmed by BICR and/or investigator.

3 BACKGROUND

3.1 Overview of Disease Pathogenesis, Epidemiology and Current Treatment

Cholangiocarcinoma is the most common biliary tract malignancy with approximately 5,000 new cases diagnosed each year in the United States (Ghouri et al 2015). The average age at presentation is 50 years, with the majority of cases in the Western world diagnosed at or after the age of 65 years (Ghouri et al 2015). Based on its location, it is classified as intrahepatic, perihilar or extrahepatic cholangiocarcinoma. Extrahepatic and perihilar cholangiocarcinoma are the most common types, with 6–8% of cholangiocarcinomas being intrahepatic, 50–67% perihilar and 27–42% distal extrahepatic (Nakeeb et al 1996; DeOliveira et al 2007).

Histologically, 90% of cholangiocarcinomas are adenocarcinomas with other variants including signet-ring type, clear cell type, papillary adenocarcinoma, intestinal type adenocarcinoma, oat cell carcinoma, adenosquamous carcinoma and squamous cell carcinoma (Olnes and Erlich 2004).

No predisposing factors are identified in most patients with cholangiocarcinoma, although there is evidence the presence of chronic inflammation, such as primary sclerosing cholangitis, hepatolithiasis, choledochal, and liver fluke infections, might be associated with the disease in some patients (National Comprehensive Cancer Network [NCCN] Guideline Version 1, 2021). Other risk factors for intrahepatic cholangiocarcinoma have been found to include infections with hepatitis C virus and/or hepatitis B virus, obesity, cirrhosis, diabetes, alcohol, non-alcoholic fatty liver disease and tobacco (Welzel et al 2007).

The clinical presentation of cholangiocarcinoma patients is unspecific. Patients with intrahepatic masses may present with abdominal pain, malaise, night sweats, weight loss and loss of appetite. Patients with extrahepatic cholangiocarcinoma tend to present with symptoms of obstructive jaundice and sometimes with complications like cholangitis (Ghouri et al 2015). There is no effective screening for cholangiocarcinoma, hence most patients with cholangiocarcinoma are diagnosed at an advanced stage.

Surgical treatments are the only potentially curative therapeutic options. For patients not amenable to curative surgical treatment, the current standard of care is combination chemotherapy with gemcitabine plus cisplatin, which has been shown to significantly increase progression free survival compared with the gemcitabine-only regimen, based on the ABC-02 trial (Valle et al 2010; Ghouri et al 2015; NCCN Guideline Version 1, 2021). In the ABC-02 trial, the median overall survival (OS) was 11.7 months in the gemcitabine with cisplatin group and 8.1 months in the gemcitabine only group. The median progression-free survival (PFS) was 8.0 months in the gemcitabine with cisplatin group and 5.0 months in the gemcitabine only group. Other gemcitabine-based and fluoropyrimidine-based combination chemotherapy regimens, including gemcitabine with

oxaliplatin or capecitabine, capecitabine with cisplatin or oxaliplatin, fluorouracil with cisplatin or oxaliplatin, and single-agent fluorouracil, capecitabine, and gemcitabine might be used (NCCN Guideline Version 1, 2021). None of these regimens are approved by the Food and Drug Administration (FDA) primarily for use in biliary tract cancers.

In the palliative setting, local ablative therapies, such as radiofrequency ablation, transarterial chemoembolization (TACE), drug eluting bead-TACE (DEB-TACE), selective intra-arterial radiotherapy with Y microspheres or external beam radiation therapy for intrahepatic cholangiocarcinoma, and photodynamic therapy with or without stents for perihilar cholangiocarcinoma, have been considered. No studies have been conducted to show the survival benefit for most of these mentioned local therapies (Ghouri et al 2015). Thus, there is a real need to develop novel therapeutic strategies for cholangiocarcinoma based on exploiting select molecular targets that would significantly impact clinical outcomes. Molecular alterations implicated in the dysregulation of cholangiocarcinoma cell growth and survival, aberrant gene expression, and invasion and metastasis have been considered potential therapeutic targets (Sirica 2005).

The fibroblast growth factor receptor (FGFR) family (FGFR 1-4) plays an important role in the pathology of cholangiocarcinoma (Jain et al 2018). Using reverse-transcriptase polymerase chain reaction screening, the FGFR2 fusion was detected in 8.9% of the patients with cholangiocarcinoma (9/102 patients), and 13.6% (9/66 patients) exclusively in the intrahepatic subtype (Borad et al 2014). Using ribonucleic acid (RNA) sequencing, Sia et al (2015) reported that FGFR2 fusions are frequent molecular aberrations in intrahepatic cholangiocarcinomas, occurring in about 16% (17/107) of patients with intrahepatic cholangiocarcinomas, and represent a recurrent targetable alteration for potential therapy.

3.2 Overview of Infigratinib

Infigratinib (formerly BGJ398, also known as BBP-831, and infigratinib phosphate) is an orally bioavailable, potent and selective ATP-competitive inhibitor of FGFRs 1-3, which has demonstrated anti-tumor activity in nonclinical in vitro and in vivo tumor models harboring FGFR genetic alterations (data on file). Infigratinib is a tyrosine kinase inhibitor and its chemical name is 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-{6-[4-(4-ethylpiperazin-1-yl)phenylamino]-pyrimidin-4-yl}-1-methylurea phosphate (1:1).

Please refer to the current Investigator's Brochure for the most recent information on infigratinib.

3.3 Nonclinical Experience with Infigratinib

At the cellular level, infigratinib selectively inhibits the kinase activity of FGFR1, FGFR2 and FGFR3, as measured by inhibition of receptor autophosphorylation, with half maximal inhibitory concentration (IC_{50}) values of 1.1, 1.0, and 2.0 nM, respectively. Infigratinib also inhibits FGFR4 (IC_{50} 61 nM), but not at clinically relevant concentrations.

Consistent with inhibition of FGFR autophosphorylation, infigratinib inhibits FGFR downstream signaling and proliferation of human cancer cell lines harboring genetic alterations of the FGFRs. These include, among others, lung and breast cancer cell lines with FGFR1 gene amplification, gastric cancer with FGFR2 gene amplification, endometrial cancer with FGFR2 mutations and bladder cancer with FGFR3 mutations or FGFR3 rearrangements (Wesche et al 2011; Guagnano et al 2012; Konecny et al 2013).

In vivo, infigratinib is widely distributed to tissues in the rat. A battery of in vivo safety pharmacology studies in rats and dogs did not reveal any effects on central nervous or respiratory systems and on hemodynamic or electrocardiographic parameters, respectively.

In repeated dose (oral gavage; up to 4-weeks) toxicity studies, infigratinib did lead to increases in serum fibroblast growth factor 23 and serum phosphorous associated with partially reversible ectopic mineralization (kidney, vascular and digestive systems) along with largely reversible changes in renal function parameters and bone growth plate thickening / retention of the primary spongiosa in rats (≥10 mg/kg/day) and dogs (≥10 mg/kg/day). These effects were deemed to be on-target effects mediated by pharmacological inhibition of FGFR.

The no observed adverse effect level in the dog and rat was 1 mg/kg.

3.4 Clinical Experience with Infigratinib

Please refer to the current Investigator's Brochure for the most recent clinical safety and efficacy information on infigratinib.

3.4.1 Clinical Pharmacokinetics and Phase 1 Data

The pharmacokinetics (PK) of infigratinib and its active metabolites have been evaluated following single and repeat daily doses in a Phase 1 study (CBGJ398X2101).

Following a single dose, median T_{max} was approximately 3-4 hours. Infigratinib had a relatively short median elimination half-life ranging from 2.69 to 5.71 hours on Day 1. Despite the relatively short half-life on Day 1, accumulation was observed with daily dosing at doses ≥60 mg, likely due to auto-inhibition of CYP3A4 mediated clearance pathways (data on file). Mean accumulation ratio (R_{acc}) ranged from 3 to 8 on Days 15 and 28. The interpatient variability was high for infigratinib.

In vitro studies indicated that infigratinib inhibits CYP3A4; therefore, a clinical drug-drug interaction study (QBGJ389-106) was conducted to assess the effects of multiple doses of infigratinib on midazolam (a sensitive CYP3A4 substrate). Midazolam exposure in terms of AUC_{inf} and C_{max} was minimally reduced (11% and 1%, respectively). For the active metabolite, 1-hydroxymidazolam, exposure increased by 19% and 26% for AUC_{inf} and C_{max}, respectively. Overall, these results indicate that infigratinib had a small effect on the metabolism of midazolam and can be considered a weak CYP3A4 inhibitor. As such, infigratinib is not expected to have a clinically relevant effect on drugs metabolized

by CYP3A4. However, due to the weak inhibition, drugs that are CYP3A4 substrates and have a narrow therapeutic index should be co-administered with caution.

In the single agent, first-in-human Phase 1 study (CBGJ398X2101), infigratinib was evaluated at 9 different dose levels and 3 different dose schedules, ranging from 5 mg/day to 150 mg/day. Eight dose levels were administered on the once daily continuous 28-day cycle schedule, and one dose level was administered on a twice a day continuous 28-day cycle schedule. One subject at 100 mg experienced Grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation, 1 subject at 125 mg daily experienced hyperphosphatemia, and 2 subjects at 150 mg experienced Grade 1 corneal toxicity (1 subject) and Grade 3 ALT and AST elevation (1 subject). The dose of infigratinib 125 mg once daily continuously was declared as the maximum tolerated dose (MTD).

While dose levels of 100 mg QD and higher were tolerated by subjects, the majority of subjects experienced reversible hyperphosphatemia, which led to study drug interruptions (data on file). An evaluation of the drug administration records for subjects prior to receiving prophylactic phosphate-lowering therapy indicated that the median time until first dose interruption was approximately 22 days and the median duration of interruption was 7 days. This observation led to the introduction of an expansion arm to evaluate the administration of 125 mg QD on a 3 week on (21 days) / 1 week off (7 days) schedule in 28-day cycles. Subjects treated with this alternative dosing schedule required less dose interruption (n=24, 49.0%) compared with subjects treated with 125 mg continuously (n=40, 70.2%). Thus, infigratinib 125 mg once daily on a 3 weeks on/1 week off schedule was declared as the recommended Phase 2 dose (RPTD).

In the dose escalation cohort of 92 subjects, no complete response (CR) was observed, and 4 subjects had partial response (PR) (1 subject at 100 mg; 3 subjects at 125 mg continuous dose).

Of the 173 subjects treated at the 125 mg continuous or intermittent schedule, CR was observed in 2 subjects (1.2%), and 22 subjects (12.7%) had PR. The overall response rate (ORR) (95% confidence interval [CI]) and disease control rate (95% CI) were 13.9% (9.10, 19.94) and 49.1% (41.47, 56.83), respectively.

The median PFS for all subjects treated at the MTD/RPTD was 3.12 months (95% CI: 2.10, 3.65 months).

3.4.2 Clinical Safety

Based on Investigator's Brochure (Edition 11), a total of 480 patients and 134 healthy volunteers had received infigratinib, alone or in combination, in 4 healthy volunteer, two Phase 1, one Phase 1b, and three Phase 2 trials. All trials have completed with the exception of the ongoing Phase 2 CBGJ398X2204 study of infigratinib in patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions/rearrangements or other FGFR genetic alterations.

A safety analysis was completed for CBGJ398X2204 on a data cutoff of 01 June 2017. As of 01 June 2017, 63 patients had been treated in CBGJ398X2204 which included 50 patients with FGFR2 fusions and 13 patients with other FGFR alterations. The most commonly reported treatment emergent adverse event (AE) of any grade was hyperphosphatemia, reported in 82.5% of patients. Other frequently reported AE include fatigue (49.2%), constipation (41.3%), stomatitis (38.1%), alopecia (38.1%), dysgeusia (31.7%), blood creatinine increased (27.0%), hypophosphatemia (27.0%), nausea (27.0%), diarrhea (25.4%), dry eye (25.4%), arthralgia (23.8%), dry mouth (23.8%), dry skin (23.8%), palmar plantar erythrodysesthesia syndrome (23.8%), aspartate aminotransferase increased (22.0%), decreased appetite (20.6%), hypercalcemia (20.6%), alanine aminotransferase increased (19.0%), vision blurred (19.0%), anemia (17.5%), dyspepsia (17.5%), vomiting (17.5%), weight decreased (17.5%), epistaxis (17.5%), onychomadesis (17.5%), myalgia (17.5%), pain in extremity (16.1%), and cough (16.1%).

Forty-one of 63 patients (65.1%) experienced at least one grade 3 or 4 event regardless of the relationship to infigratinib. Grade 3 or 4 events that occurred in at least 5% of patients were hyperphosphatemia (15.9%), hypophosphatemia (6.3%), hyponatremia (12.7%), lipase increased (7.9%), and stomatitis (7.9%).

Twenty-nine of 63 patients (46.0%) experienced at least one grade 3 or 4 suspected to be related to infigratinib. Grade 3 or 4 events that occurred in at least 5% of patients were hyperphosphatemia (15.9%) and stomatitis (7.9%).

Overall, most AEs reported have been mild to moderate in severity, reversible, and unrelated to infigratinib.

No effect of infigratinib on electrocardiogram (ECG) intervals, including QTc, has been noted. Reversible and largely asymptomatic decreases in left ventricular ejection fraction (LVEF) have been noted in subjects enrolled on study, as measured by serial transthoracic echocardiography or multiple gated acquisition (MUGA) scans.

3.4.3 Clinical Efficacy

Preliminary anti-tumor activity was seen in the Phase 1 first-in-human trial in subjects treated at doses of ≥100 mg of infigratinib in FGFR1-amplified squamous non-small cell lung cancer and urothelial carcinoma with FGFR3 genetic alterations.

As of 08 August 2018, 83 subjects with advanced or metastatic cholangiocarcinoma containing FGFR genetic alterations were enrolled in Study CBGJ398X2204, of whom 71 had FGFR2 fusions or rearrangements. Of 71 evaluable subjects with the potential for confirmation of response (subject completed or discontinued prior to 6 cycles) (preliminary data with a cutoff date of 08 August 2018), the investigator-assessed ORR was 26.9% (95% CI: 16.8-39.1%). The disease control rate (CR + PR + stable disease [SD]) was 83.6% (95% CI: 72.5-91.5%), with a median duration of response of 5.4 months (95% CI: 3.7-7.4 months). The median PFS was 6.8 months (95% CI: 5.3-7.6 months) (Javle et al 2018).

3.5 Rationale

3.5.1 Study Rationale and Purpose

The growing understanding of the genetic alterations involved in the tumorigenesis of cholangiocarcinoma provides new therapeutic options for molecular targets. Among other genetic alterations, recurrent fusions involving the FGFRs are an important class of driver mutations in a number of tumor types, including cholangiocarcinoma.

Wu et al (2013) reported 24 primary tumors or cell lines with FGFR1, FGFR2, or FGFR3 fusions among other targetable fusions. These FGFR fusions involve numerous protein partners with various functions that maintain kinase activity after formation. The identified fusions expressed an FGFR family member as a 5' or 3' fusion partner with an intact kinase domain, suggesting that these may serve as potential therapeutic targets via kinase inhibition. Cancer types harboring FGFR fusions were quite diverse and included cholangiocarcinoma (n=2), breast cancer (n=4), prostate cancer (n=1), thyroid cancer (n=1), lung squamous cell carcinoma (n=6), bladder cancer (n=5), oral cancer (n=1), head and neck squamous cell carcinoma (n=2), and glioblastoma (n=2). Two cholangiocarcinoma patients were reported to harbor FGFR2-bicaudal c homolog 1 (BICC1) fusions. Cells harboring FGFR fusions showed enhanced sensitivity to the FGFR inhibitors PD173074 and pazopanib, suggesting that patients with cancer with FGFR fusions may benefit from targeted FGFR kinase inhibition.

In a second study (Arai et al 2014), two fusion kinase genes, FGFR2-AHCYL1 and FGFR2-BICC1 were identified in 2 of 8 cholangiocarcinoma tumor samples by massive-parallel whole transcriptome sequencing. Further, reverse transcription polymerase chain reaction and Sanger sequencing analysis of 102 cholangiocarcinoma specimens (66 intrahepatic cholangiocarcinomas and 36 extrahepatic cholangiocarcinomas) identified seven FGFR2-AHCYL1-positive and two FGFR2-BICC1-positive cases, which were identified as oncogenic in an NIH3T3 transformation assay. Treatment with FGFR inhibitors, including infigratinib, reversed the transformed phenotype. In a third study (Jiao et al 2013), somatic mutations in FGFR2 were identified in 4 of 32 (12.5%) intrahepatic cholangiocarcinomas. Thus, FGFR fusions or activating mutations could potentially identify a subset of cholangiocarcinoma patients who would benefit from targeted FGFR kinase inhibition.

Infigratinib has been shown to specifically inhibit proliferation of cancer cells with FGFR genetic alterations; infigratinib did not alter cell growth in cells that did not express FGFR or where FGFR was not altered (data on file). In vivo, infigratinib significantly inhibited growth of tumors in a dose-dependent manner in various mouse and rat xenograft subcutaneous or orthotopic models. These include models of bladder cancer with FGFR3 chromosomal rearrangement or FGFR3 mutation (RT112, MGHU3), endometrial cancer with FGFR2 mutation (AN3CA), lung cancer with FGFR1 amplification (NCI-H1581) and gastric cancer with FGFR2 amplification (SNU16) (data on file).

On the basis of the activity of infigratinib in a variety of cancer models harboring FGFR genetic alterations (Guagnano et al 2012), including rearrangements, the Phase 2 study CBGJ398X2204 was conducted. As described above, the single arm study demonstrated clinically meaningful activity of infigratinib in subjects with refractory cholangiocarcinoma containing FGFR2 fusions or other rearrangements.

3.5.2 Rationale for the Study Design

The ABC-02 trial established gemcitabine with cisplatin as standard of care for first line treatment of cholangiocarcinoma (Valle et al 2010). Still, the median PFS was 8.0 months and median OS was 11.7 months. Study CBGJ398X2204 suggested that infigratinib could offer a targeted, chemotherapy-free therapeutic option for first line treatment of patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions.

The current Phase 3 study is being conducted to evaluate the efficacy and safety of infigratinib specifically in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion/rearrangement. Further, PK estimates will be evaluated to gain further understanding of the PK of infigratinib and its metabolites. In addition to the companion diagnostic detection of molecular alterations, longitudinal tumor and blood samples from treated subjects will be analyzed. Molecular characterization of tumors at baseline and at the time of progression may allow for increased understanding of potential treatment combinations, as well as primary and acquired resistance mechanisms.

The study is of parallel-group design, comparing orally administered infigratinib with infusion of gemcitabine plus cisplatin (recommended by the NCCN as first line treatment of advanced biliary tract cancer [NCCN Guideline Version 1, 2021]). The study is stratified and randomized to prevent bias. The study is open-label, as a double-dummy design is not ethically feasible.

3.5.3 Rationale for Dose and Regimen Selection

In this study, subjects randomized to the infigratinib group will receive 125 mg QD of infigratinib on a 3 week on (21 day) /1 week off (7 day) schedule in 28-day cycles. This dose level and regimen is based on experiences from the Phase 1 CBGJ398X2101 and Phase 2 CBGJ398X2204 trials, described in Section 3.4. Subjects with mild/moderate renal or hepatic impairment should have their dose adjusted because the relative potency adjusted steady state AUC of infigratinib and its metabolites is increased in these subjects compared with that for subjects with normal organ function; see Section 7.2.1 for dosing recommendations, and see the current Investigator's Brochure for recent clinical safety updates.

Subjects in the gemcitabine plus cisplatin group will receive intravenous (IV) infusions of gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2), according to each country's respective labeling, local institutional practices, the ABC-02 trial (Valle et al 2010), and as recommended by the NCCN and European Society of Medical Oncology (ESMO) guidelines as first line treatment of advanced biliary tract cancer. Subjects who

experience progressive disease (PD) in the gemcitabine plus cisplatin group will be offered the opportunity to receive infigratinib upon PD confirmed by BICR (NCCN Guideline Version 1, 2021; Valle et al 2016).

3.6 Benefit/Risk Assessment

Cholangiocarcinoma harboring FGFR2 fusion/rearrangement, for which standard anticancer therapies are still not available, represent a targetable disease for potential therapy with infigratinib. Novel chemotherapy-free, oral treatment options with durable, clinically meaningful benefit would be a significant improvement over available treatments for patients with cholangiocarcinoma harboring FGFR2 fusions/rearrangements.

The nonclinical pharmacologic, PK, and toxicologic properties of infigratinib have been thoroughly evaluated and support the use of infigratinib in patients with advanced cancer. These nonclinical data support investigation of infigratinib as a therapy for tumors with oncogenic FGFR2 activation, including cholangiocarcinoma.

Infigratinib has shown evidence of clinical activity in adult patients with unresectable locally advanced or metastatic cholangiocarcinoma, supporting its efficacy (as described in Section 3.4.3 and in the Investigator's Brochure), and infigratinib had an acceptable safety profile in this population. Reported adverse events across the infigratinib development program are consistent with its mechanism of action and can be adequately managed/reversed through dose modification and supportive care, thus minimizing risk to study subjects who receive infigratinib. Available clinical data support investigation of the safety and efficacy of infigratinib in cholangiocarcinoma.

Subjects will be closely monitored for safety. For adult patients with cancer who were treated with infigratinib, hyperphosphatemia and ocular events are important identified risks. Safety assessments consist of complete ophthalmic exams including optical coherence tomography (OCT) and performance status assessments. Serum phosphorus will be monitored. Based on the mechanism of action and findings in animal reproduction studies, infigratinib may cause embryo-fetal harm or loss of pregnancy when administered to a pregnant woman. Pregnant women and females of reproductive potential are advised of the potential risk to a fetus. Pregnancy status in females of reproductive potential will be verified prior to initiating infigratinib. Females of reproductive potential will be advised to use effective contraception during treatment with infigratinib and for 1 month after the last dose. Males that are partnered with females of reproductive potential will be advised to use effective contraception during treatment with infigratinib and for 1 month after the last dose.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of infigratinib may be found in the current Investigator's Brochure.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with infigratinib are justified by the anticipated benefits that may be afforded to subjects with cholangiocarcinoma.

4 OBJECTIVES AND ENDPOINTS

4.1 Objectives

The primary objective is to determine if treatment with infigratinib improves PFS as assessed by BICR compared to treatment with gemcitabine and cisplatin in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion/rearrangement.

The secondary objectives are to

- Determine if treatment with infigratinib improves OS compared to treatment with gemcitabine and cisplatin in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion/rearrangement.
- Evaluate the efficacy of infigratinib treatment compared to gemcitabine and cisplatin in terms of investigator assessed PFS.
- Further evaluate the efficacy in subjects treated with infigratinib versus gemcitabine and cisplatin by ORR, best overall response (BOR), duration of response and disease control rate determined by BICR and by the investigator.
- Characterize the safety and tolerability of single agent infigratinib.

The exploratory objectives are to

- Evaluate the efficacy of infigratinib treatment compared to gemcitabine and cisplatin in terms of investigator assessed PFS after subsequent therapy (PFS2).
- Compare quality of life (QOL) in subjects treated with infigratinib or gemcitabine and cisplatin.
- Assess the PK of infigratinib and its active metabolites including BHS697 and CQM157.
- Evaluate the overall genomic landscape of subjects with cholangiocarcinoma.
- Evaluate biomarkers related to cholangiocarcinoma biology and their potential correlation to efficacy, disease progression, and resistance to study medications.

4.2 Endpoints

The primary endpoint is PFS (from date of randomization until date of progression as determined by blinded independent central review [BICR] or death due to any cause, whichever is earlier).

The secondary endpoints are:

- OS (from date of randomization until date of death)
- PFS as determined by the investigator
- ORR assessed by BICR according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
- ORR assessed by the investigator according to RECIST Version 1.1
- BOR, disease control rate (PR + CR + SD), and duration of response (only for subjects who have a response) assessed by BICR and by the investigator according to RECIST 1.1
- Type, frequency, and severity of AEs and serious AEs (SAEs), laboratory abnormalities, and other safety findings.

The exploratory endpoints are:

- PFS2 (from date of randomization until date of progression on the subsequent therapy or death due to any cause, whichever is earlier) as determined by the investigator
- QOL as measured by the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) C30, EORTC QLQ-BIL21, and EuroQOL five dimensions questionnaire (EQ-5D)
- PK parameters (C_{max}, C_{min}, and R_{acc})
- The prevalence of genomic alterations and their correlations with available clinicopathologic and demographic features in subjects with cholangiocarcinoma
- Genomic and proteomic assessments of tumor biopsies and cell-free DNA (blood) at baseline, during treatment, and at disease progression; and determination of the prognostic and/or predictive value of biomarkers to the clinical endpoints.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is a multi-center, open label, randomized, controlled Phase 3 study to determine if treatment with infigratinib improves PFS assessed by BICR (primary objective) and OS (key secondary objective) compared to treatment with gemcitabine and cisplatin in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion/rearrangement. The study will be conducted at approximately 145 study centers worldwide.

For the purposes of this protocol, “advanced/metastatic or inoperable” (as in the protocol title) is equivalent to “unresectable locally advanced or metastatic” (protocol-defined study population).

A study schematic is presented in Figure 1.

Subjects will be randomized in a 2:1 ratio to receive oral infigratinib administered once daily for the first 3 weeks (21 days) of a 28-day treatment cycle compared to a regimen of gemcitabine with cisplatin given on Days 1 and 8 of a 21-day treatment cycle (see Section 7.1 for details). Randomization will be stratified by unresectable locally advanced vs metastatic disease, geographic region (North America, Western Europe, Asia Pacific, and rest of the world), prior neoadjuvant/adjuvant treatment (yes/no), and received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no).

During the treatment period, subjects will be radiographically evaluated every 8 weeks ±7 days from the first dose of study drug, regardless of drug interruption, for tumor response using the RECIST 1.1 criteria. When the decision is made to discontinue study drug (see Section 8.1.1 for details), subjects will complete an End of Treatment (EOT) visit, no later than 8 days from the decision to discontinue study drug, and a Safety Follow-up visit no more than 30 days after last dose of study drug. If a subject discontinues study drug for reasons other than radiographic PD confirmed by BICR, a radiographic assessment should be conducted at the EOT visit, unless taken within the previous 4 weeks.

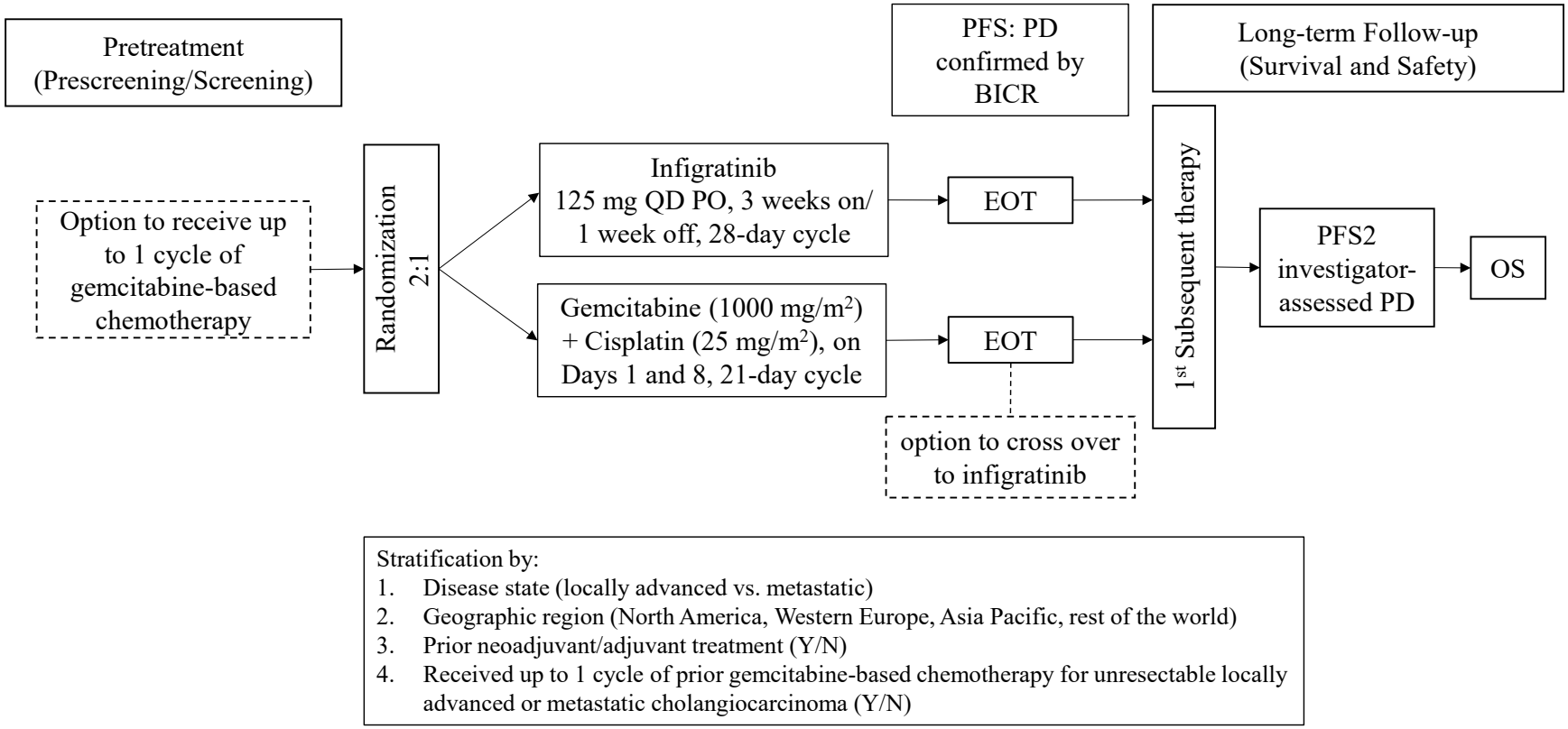
Subjects who discontinue study drug for radiographic PD confirmed by BICR will be followed approximately every 3 months (via telephone or office visit) for survival status and new anticancer therapy information (subsequent therapy and progression/PFS2) until End of Study (EOS), defined as the time when at least 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment. Subjects who discontinue study drug for reasons other than PD confirmed by BICR will continue to have radiographic assessments every 8 weeks ±7 days until radiographic PD confirmed by BICR. Thereafter, these subjects will be followed approximately every 3 months for survival status and use of anticancer therapy, as described above.

Sparse PK blood samples will be collected from all subjects in the infigratinib group at multiple time points, predose (C_{min} infigratinib) and 4 hours (±30 minutes) postdose (C_{max} infigratinib). Plasma concentrations of infigratinib and its metabolites (including BHS697 and CQM157) will be measured.

For a PK substudy, blood samples will be collected, at multiple time points (predose [C_{min} infigratinib], 4 hours [±30 minutes] postdose, and 24 hours postdose [±1 hour]) from the first 40 subjects who receive infigratinib. Plasma concentrations of infigratinib and its active metabolites (including BHS697 and CQM157) will be measured.

Subjects randomized to the gemcitabine with cisplatin group may be eligible to cross over and receive infigratinib following radiographic PD confirmed by BICR; these subjects will be followed for safety and OS (according to the schedule of assessments in Table 5).

Figure 1: Study Design



Abbreviations: BICR, blinded independent central review; EOT, end of treatment; N, no; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, PFS on subsequent therapy; PO, oral; QD, once daily; Y, yes.

5.2 Number of Subjects and Time on Study

Approximately 300 subjects with a likely or known activating FGFR2 fusion/rearrangement determined by a central laboratory or local laboratory are planned for study participation. Note: Central laboratory determination of FGFR2 fusion/rearrangement is required for all subjects but local determination of FGFR2 fusion/rearrangement may be obtained and used for eligibility and randomization prior to central laboratory results being available. If available FGFR2 fusion/rearrangement determination is from the central laboratory being used in the study, a tumor sample does not need to be submitted for central FGFR2 fusion/rearrangement molecular testing.

The duration of time spent on study will vary by subject. Each subject will have a Screening visit, conducted up to 28 days prior to first dose of study drug. Thereafter, subjects will receive study drug until radiographic PD confirmed by BICR, unacceptable toxicity, or other reason listed in Section 8.1.1. Following radiographic PD confirmed by BICR, subjects in the gemcitabine with cisplatin group may be eligible to cross over and receive infigratinib.

Once study drug is discontinued, subjects are to complete an EOT visit, followed by 30-day Safety Follow-up visit. Thereafter, subjects will be followed for disease progression and/or survival status, as previously described.

6 STUDY POPULATION

6.1 Inclusion Criteria

To be eligible for the study, subjects must meet all of the following criteria:

1. Have histologically or cytologically confirmed unresectable locally advanced or metastatic cholangiocarcinoma. Subjects with gallbladder cancer or ampulla of Vater carcinoma are not eligible.

2. Have written documentation of local laboratory or central laboratory determination of a known or likely activating FGFR2 fusion/rearrangement from a sample collected before randomization (refer to Section 10.3.1 for the definition of a known or likely activating FGFR2 fusion/rearrangement). Note: All subjects enrolled based on local molecular test results must have sufficient tumor tissue for confirmation of FGFR2 fusion/rearrangement by the central laboratory, but this central confirmation is not required prior to enrollment in the study.

3. Have an archival tumor tissue sample available with sufficient tumor content for FGFR2 fusion/rearrangement molecular testing by the central laboratory. However, if an archival tumor tissue sample is not available or does not meet requirements for central testing, a newly obtained (before randomization) tumor biopsy may be submitted instead. If a prestudy written documentation of FGFR2

fusion/rearrangement in tumor tissue is available from the central laboratory, an additional tumor sample does not need to be submitted.

4. Have full recovery from the following permitted prior treatments (as applicable) such that the subject is reasonably expected to tolerate study treatment (gemcitabine/cisplatin or infigratinib) according to the investigator's assessment:
   a. A non-curative operation (ie, R2 resection [with macroscopic residual disease] or palliative bypass surgery only)
   b. Curative surgery with evidence of unresectable disease relapse requiring systemic chemotherapy
   c. Adjuvant radiotherapy (with or without radio-sensitizing low-dose chemotherapy) for localized disease provided there has been clear evidence of disease progression before inclusion in this study
   d. Adjuvant or neoadjuvant chemotherapy, provided recurrence occurred >6 months after the date of the last dose of adjuvant or neoadjuvant therapy and before randomization
   e. Gemcitabine-based chemotherapy (specified in Appendix 5 [Section 17.5]) for advanced/unresectable or metastatic cholangiocarcinoma (≤1 cycle)
      i. Recovery from acute toxicities to the extent that would allow initiation of cisplatin-gemcitabine (absolute neutrophil count (ANC) ≥1,000/mm^3 (≥1.0 × 10^9/L); platelets ≥100,000/mm^3 (≥100× 10^9/L)
      ii. Baseline tumor assessment at least 7 days after the last dose of chemotherapy and before randomization
      iii. The window between the last dose of chemotherapy and the start of randomized study treatment must be ≥14 days and ≤5 weeks
   f. Photodynamic treatment provided there is clear evidence of disease progression at the local site or at a new metastatic site

5. Are ≥18 years of age of either gender.

6. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤1.

7. Have a life expectancy >3 months.

8. Are able to read and/or understand the details of the study and provide written evidence of informed consent as approved by IRB/IEC.

9. Are able to swallow and retain oral medication.

10. Are willing and able to comply with scheduled visits, treatment plan and laboratory tests.

11. If a woman of childbearing potential (WOCBP), must have a negative pregnancy test within 7 days of the first dose of study drug. A woman is not of childbearing potential if she has undergone surgical sterilization (total hysterectomy, or bilateral tubal ligation or bilateral oophorectomy at least 6 weeks before taking study drug) or if she is postmenopausal and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for at least 12 months, with an appropriate clinical profile, and there is no other cause of amenorrhea (eg, hormonal therapy, prior chemotherapy).

    WOCBP and males whose sexual partners are WOCBP must agree to use barrier contraception and a second form of highly effective contraception (Clinical Trials Facilitation Group 2014; see Appendix 3 [Section 17.3]) while receiving study drug and for 1 month following their last dose of infigratinib or 6 months following their last dose of gemcitabine/cisplatin (or according to local labeling and standard institutional practice). Alternatively, total abstinence is also considered a highly effective contraception method when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    Sexually active males must use a condom during intercourse while taking drug and for 1 month after the last dose of infigratinib or 6 months after their last dose of gemcitabine/cisplatin (or according to local labeling and standard institutional practice) and should not father a child during this period. A condom is required to be used by vasectomized men and by men having intercourse with a male partner, to prevent delivery of the drug via seminal fluid.

6.2 Exclusion Criteria

To be eligible for the study, subjects must not meet any of the following criteria:

1. Have received treatment with any systemic anti-cancer therapy for unresectable locally advanced or metastatic cholangiocarcinoma, with the following exceptions:
    a. Prior neoadjuvant or adjuvant therapy is permitted if documented disease recurrence occurred ≥6 months after the last date of neoadjuvant or adjuvant therapy
    b. One cycle of gemcitabine-based chemotherapy (specified in Appendix 5 [Section 17.5]) for locally advanced or metastatic cholangiocarcinoma is permitted before randomization

2. Have history of a liver transplant.

3. Have previously or currently is receiving treatment with a mitogen-activated protein kinase (MEK) or selective FGFR inhibitor.

4. Have neurological symptoms related to underlying disease requiring increasing doses of corticosteroids. Note: Steroid use for management of central nervous system

tumors is allowed but must be at a stable or decreasing dose of corticosteroids for at least 2 weeks preceding randomization.

5. Have a history of another primary malignancy within 3 years except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin or any other curatively treated or surveilled malignancy (eg, localized low-risk prostate cancer) that is not expected to require treatment for recurrence during the course of the study.

6. Have any other medical condition that would, in the investigator's judgment, prevent the subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures.

7. Have current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis, or diabetic retinopathy, confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.

8. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, vascular system, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification.

9. Have impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).

10. Have current evidence of endocrine alterations of calcium/phosphate homeostasis, eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis, etc.

11. Are currently receiving or are planning to receive during participation in this study, treatment with agents that are known moderate or strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone. See Appendix 2 (Section 17.2) for details.

12. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits within 7 days prior to first dose of study drug.

13. Have insufficient bone marrow function:
    a. Absolute neutrophil count (ANC) <1,000/mm^3 (1.0×10^9/L)
    b. Platelets <100,000/mm^3 (<100×10^9/L)

c. Hemoglobin <8.5 g/dL; transfusion support is allowed if >1 week before randomization and hemoglobin remains stable

14. Have insufficient hepatic and renal function:
    a. Total bilirubin >1.5 × upper limit of normal (ULN) (for patients with documented Gilbert syndrome, direct bilirubin ≤1.5 × ULN and enrollment requires approval by the medical monitor)
    b. AST/ serum glutamic-oxaloacetic transaminase (SGOT) and ALT/ serum glutamic-pyruvic transaminase (SGPT) >2.5 × ULN (AST and ALT >5 × ULN in the presence of liver involvement of cholangiocarcinoma)
    c. Calculated (using the Cockcroft-Gault formula [Cockcroft and Gault 1976]) or measured creatinine clearance of <45 mL/min (or value ≥45 mL/min that excludes administration of cisplatin per local label and institutional guidelines)
15. Have amylase or lipase >2.0 × ULN
16. Have elevated phosphorus or abnormal serum calcium, or calcium-phosphorus product ≥55 mg^2/dL^2 (refer to Section 9.3 for guidance on calculation):
    a. Inorganic phosphorus >1.1 × ULN
    b. Total corrected serum calcium >11 mg/dL or <8 mg/dL
17. Have clinically significant cardiac disease including any of the following:
    a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥2B) or uncontrolled hypertension (refer to the European Society of Cardiology and European Society of Hypertension guidelines [Williams et al 2018])
    b. Presence of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade ≥2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality
    c. Unstable angina pectoris or acute myocardial infarction ≤3 months prior to first dose of study drug
    d. QTcF >470 msec (males and females). Note: If the QTcF is >470 msec in the first ECG, a total of 3 ECGs separated by at least 5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤470 msec, the subject meets eligibility in this regard
    e. Known history of congenital long QT syndrome
18. Have had a recent (≤3 months prior to first dose of study drug) transient ischemic attack or stroke
19. CTCAE (v5.0) Grade ≥2 hearing loss
20. CTCAE (v5.0) Grade ≥2 neuropathy

21. If female, is pregnant or nursing (lactating), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or blood laboratory test.

22. Have known microsatellite instability-high (MSI-H) disease and the decision is made by the treating investigator that an alternative, non-study therapy is warranted according to standard of care.

23. Have any known hypersensitivity to gemcitabine, cisplatin, calcium-lowering agents, infigratinib, or their excipients.

24. Have any contraindication to cisplatin or gemcitabine treatment according to local labeling or standard institutional practice.

25. Have taken any Chinese herbal medicine or Chinese patent medicine treatments with anticancer activity within 14 days of the first dose of study drug.

26. Have received a live vaccine within 30 days before the first dose of study drug or are planning to receive a live vaccine during participation in this study.

7 TREATMENTS

7.1 Treatments Administered

Subjects randomized to the infigratinib group will receive hard gelatin capsules for oral infigratinib 125 mg QD (administered as one 100-mg capsule and one 25-mg capsule) using a "3 weeks on, 1 week off" schedule for each 28-day treatment cycle. Subjects with mild/moderate renal or hepatic impairment should have their dose adjusted; see Section 7.2.1 for dosing recommendations. Infigratinib treatment will continue until radiographic PD confirmed by BICR, unacceptable toxicity, or other reason listed in Section 8.1.1. Subjects who cross over to infigratinib will continue on treatment until a criterion listed in Section 8.1.1 is met.

Subjects randomized to the gemcitabine with cisplatin group will receive IV infusions of gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on an outpatient basis according to each country's respective labeling and local institutional practices. The gemcitabine and cisplatin infusions will be administered on Days 1 and 8 of each 21-day treatment cycle until radiographic PD confirmed by BICR; unacceptable toxicity; or other reason listed in Section 8.1.1. Following radiographic PD confirmed by BICR, subjects randomized to the gemcitabine with cisplatin group may be eligible to cross over and receive infigratinib.

If a subject cannot tolerate cisplatin, they can remain on gemcitabine alone. However, if gemcitabine is discontinued due to toxicity, then all study treatment must be discontinued. The subject will have an EOT visit within 8 days of the decision to discontinue study drug, and a Safety Follow-up visit no more than 30 days after last dose

of study drug. Thereafter, subjects will be followed for disease progression and survival (as previously described).

7.2 Information on Infigratinib

7.2.1 Subject Instructions for Infigratinib Dosing

Subjects with mild or moderate renal impairment (creatinine clearance 30 mL/min to ≤89 mL/min) should be administered a starting dose of 100 mg QD infigratinib on a 3 week on (21 day) /1 week off (7 day) schedule. Subjects with mild (total bilirubin >ULN to 1.5×ULN or AST >ULN) and moderate hepatic impairment (total bilirubin >1.5 to 3×ULN with any AST) should be administered a starting dose of 100 and 75 mg QD of infigratinib, respectively, on a 3 week on (21 day) /1 week off (7 day) schedule. For subjects with combined hepatic and renal impairment, the lower of the 2 starting doses should be administered.

Subjects in the infigratinib group should be instructed to take the daily dose of infigratinib in the morning, at approximately the same time each day (24 ±4 hour interval). Subjects will take their first dose of infigratinib at the study center on Cycle 1 Day 1. On the days of PK sampling, subjects should not take their study drug dose at home; subjects should take their study drug with them to the study center where dosing of infigratinib will be supervised and administration time recorded. On PK sampling days after Cycle 1 Day 1, the time of the previous infigratinib administration (ie, the prior day) before the pre-dose PK sample will be recorded in the eCRF. Administration may fall outside of the ±4 hour interval on the days of PK sampling.

Infigratinib should be taken in the fasted state at least 1 hour before or 2 hours after a meal. It should be taken with a large glass of water (~250 mL) and consumed over as short a time as possible. Subjects should be instructed to swallow the capsules whole and not chew them.

If the subject forgets to take the scheduled dose of infigratinib in the morning (other than on a day of PK sampling), he/she should not take the dose more than 4 hours after the usual time and should continue treatment the next day. Any such doses that are missed should be skipped altogether and should not be replaced or made up at the next scheduled dosing.

If vomiting occurs following dosing with infigratinib, re-dosing is not permitted the same day. Dosing should resume the next day. If vomiting occurs on a PK sampling day within the first 4 hours postdosing, this event is to be noted on the Dose Administration page of the electronic case report form (eCRF), as well as on the AE page, as appropriate.

Infigratinib is characterized by pH-dependent solubility; therefore, medicinal products that alter the pH of the upper GI tract may alter the solubility of infigratinib and limit bioavailability. These agents include, but are not limited to, proton pump inhibitors (eg, omeprazole), H2-antagonists (eg, ranitidine) and antacids. Proton pump inhibitors are prohibited due to their long pharmacodynamic effect and should be replaced with

H2-antagonists or antacids. Infigratinib should be taken at least 2 hours before or 10 hours after dosing with H2-antagonists. Antacids, locally acting acid neutralizing agents, are to be separated from infigratinib doses by 2 hours.

Subjects in the infigratinib group must avoid the consumption of grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or juice within 7 days prior to the first dose of infigratinib and throughout the treatment period. This is due to a potential CYP3A4 interaction with study drug. Normal oranges and orange juice are allowed.

7.2.2 Description and Dispensing of Infigratinib

Infigratinib will be supplied as hard gelatin capsules for oral use at dose strengths of 25 and 100 mg. Excipients will include microcrystalline cellulose, lactose monohydrate, hypromellose 2910, crospovidone, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule. Infigratinib will be manufactured under Good Manufacturing Practice for investigational use. The color and appearance of the capsules are outlined below.

Physical Attribute	Appearance (color)	Size 3 Capsule: White opaque body with gray opaque cap, imprinted with a green band on the body and a black band on the cap filled with white to greyish powder (25 mg) Size 1 Capsule: White opaque body with light orange opaque cap, imprinted with a green band on the body and a black band on the cap filled with white to greyish powder (100 mg)

Infigratinib will be provided in 21-count bottles (FMI IV formulation).

The site pharmacist or designee will dispense the correct number and dose strength of capsules to ensure the subject receives sufficient drug for each 28-day treatment cycle. Study drug will be dispensed to the subject by authorized trained site personnel only.

7.2.3 Packaging and Labeling

Infigratinib capsules will be packaged in high density polyethylene bottles with intact induction seal child resistant closures. Study drug labels will be in the local language and comply with the legal requirements of each country. Labels will include storage conditions for the drug.

7.2.4 Study Drug Accountability, Handling, and Disposal

Infigratinib capsules will be received by designated personnel at the study center, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, infigratinib should

be stored according to the instructions specified on the drug label and in the Investigator's Brochure. Refer to the Pharmacy Manual for further details.

The investigator or designee must maintain an accurate record of the shipment and dispensing of infigratinib in a drug accountability log. Subjects in the infigratinib group will be asked to return all used and unused bottles of infigratinib and packaging on a regular basis, at the end of the study, or at the time of study drug discontinuation. Drug accountability will be assessed by the investigator and/or study personnel, and captured in a subject drug accountability log. This information must be captured in the source document at each subject visit. Drug accountability will be completed by the field monitor during study center visits and at the completion of the study.

At study close-out, and, as appropriate during the course of the study, the investigator will provide access to all used and unused bottles of infigratinib, packaging, drug labels, and a copy of the completed drug accountability log to the field monitor.

At study close-out, infigratinib can be destroyed at the study center if permitted by local regulations. Alternatively, the study drug can be destroyed at a third party depot.

7.2.5 Dose Modifications for Infigratinib

Subject management will be based upon investigator evaluations.

7.2.5.1 Dose Modifications and Delays

For subjects who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the subject to continue infigratinib. For these subjects, the dosing guidelines outlined below will be followed. All dose modifications related to tolerability should be based on the worst preceding toxicity, as described in Table 7 (AEs considered possibly related to infigratinib) and Table 9 (skin toxicity). In addition, according to investigator's medical judgment, dose modification (hold) can be applied for subject safety (eg, perioperatively); a sponsor medical monitor must be consulted for dose modifications that are not related to tolerability. Dosage changes must be recorded on the appropriate page of the eCRF.

The following guidelines should be applied.

- Each subject may be allowed up to 3 infigratinib dose reductions according to protocol specified dose modifications for AEs. Dose reductions below 50 mg are not allowed. Prospective sponsor medical monitor approval is required for the third dose reduction (Table 6).

- Management of related toxicity, including during a period of infigratinib hold, will continue until the toxicity is stable at Grade ≤1, returns to baseline, or is in accordance with the assessment of the treating physician.

If treatment is resumed at the same dose of infigratinib, and the same toxicity recurs with the same or worse severity regardless of duration, dose must be reduced to the next lower dose level. If treatment is resumed at the lower dose of infigratinib, and the same toxicity recurs with the same or worse severity, the subject should have a second dose reduction.

- Subjects who permanently discontinue infigratinib for a study related AE or an abnormal laboratory value must be followed as described in Section 7.2.5.2.

- Study drug must be permanently discontinued for a delay of >14 days and may only be restarted with written permission of a sponsor medical monitor if (1) the delay was not due to an AE that requires permanent infigratinib discontinuation as provided in Table 7, and (2) the subject has not met other criteria requiring infigratinib discontinuation as provided in Section 8, and it is the Investigator's opinion that no safety concerns are present. In situations where a delay of >14 days is needed for a treatment-related AE requiring permanent infigratinib discontinuation (see Table 7), with prospective sponsor medical monitor approval, the delay may be extended to a maximum of 28 days before permanent treatment discontinuation is required.

- If infigratinib is on hold for ≤14 days, and the criteria for restarting treatment are met, infigratinib can be restarted on Day 1 to Day 21 of a cycle. Study drug should not be restarted on Day 22 to Day 28 of a cycle; in such cases, treatment restart must wait until Day 1 of the next cycle.

Table 6: Dose Reduction Scheme for Infigratinib

Dose Reduction				
	Starting dose level 0	Dose level -1	Dose level -2	Dose level -3
Infigratinib	125 mg	100 mg	75 mg	50 mg [a]

[a] Dose reduction to 50 mg requires prospective sponsor medical monitor approval. Details are provided in the text above.

Table 7: Criteria for Interruption and Re-initiation of Infigratinib for Adverse Events Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE[a] (v5.0) Grade (Unless Otherwise Specified)	Dose Modifications any Time During a Cycle of Therapy
CARDIAC DISORDERS	
Cardiac - Prolonged QTc Interval	
Grade 2: Average QTc 481-500 msec	Maintain dose level of infigratinib. Two additional ECGs separated by at least 5 minutes should be performed to confirm the finding. If the finding is confirmed, single ECG assessments should be performed for 2 additional cycles at the same frequency as in Cycle 1, or as clinically indicated. If abnormality is detected, 2 additional ECGs separated by at least 5 minutes should be performed to confirm the finding. • If ECG assessments show no QTcF ≥481 msec, for subsequent cycles ECG monitoring will be performed as according to the visit schedule. • If ECG assessments are still abnormal (QTcF ≥481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in Cycle 1 for all subsequent cycles.
Grade 3: Average QTc ≥501 msec; >60 msec change from baseline	Hold dose of infigratinib. Two additional ECGs separated by at least 5 minutes should be performed to confirm the finding. If the finding is confirmed, monitor subject with hourly ECGs until the QTcF has returned to baseline and perform further monitoring as clinically indicated. • Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesaemia and decreased blood oxygenation. • Subjects should receive appropriate electrolyte replacement and should not receive further infigratinib until electrolytes are documented to be within normal limits. Once the QTcF prolongation has resolved to <481 msec, subjects may be re-treated at one lower dose level at the investigator's discretion. If not determined to be clinically significant, the subject may resume at the current dose. Single ECG assessments should be performed for 2 additional cycles at the same frequency as in Cycle 1 or as clinically indicated. If abnormality is detected, 2 additional ECGs separated by at least 5 minutes should be performed to confirm the finding. • If ECG assessments show no QTcF ≥481 msec, ECG monitoring will be performed as according to the visit schedule for subsequent cycles. • If ECG assessments are still abnormal (QTcF ≥481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in Cycle 1 or as clinically indicated, for all subsequent cycles. • Subjects who experience recurrent QTcF ≥501 msec after one dose reduction will be discontinued from infigratinib.

Worst Toxicity CTCAE[a] (v5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
Grade 4: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Discontinue infigratinib.
INVESTIGATIONS-HEMATOLOGY	
Neutrophil Count Decreased (Neutropenia)	
Grade 3 (ANC <1000-500/mm^3 [<1.0–0.5 × 10^9/L])	Hold dose of infigratinib until resolved to CTCAE Grade ≤1 or baseline, then • If resolved within ≤7 days, maintain dose level of infigratinib • If resolved between >7 days and 14 days, ↓ 1 dose level of infigratinib • If not resolved within ≤14 days, discontinue infigratinib
Grade 4 (ANC <500/mm^3 [<0.5 × 10^9/L])	Hold dose of infigratinib until resolved to CTCAE ≤Grade 1, then ↓ 1 dose level of infigratinib • If not resolved within ≤14 days, discontinue infigratinib
Febrile Neutropenia	
Grade 3 (ANC <1000 mm^3 with a single temperature of >38.3°C [101.0°F] or a sustained temperature of ≥38.0°C [100.4°F] for >1 hour)	Hold dose of infigratinib until resolved to CTCAE Grade ≤1, then • If resolved within ≤14 days, ↓ 1 dose level of infigratinib • If not resolved within 14 days, discontinue infigratinib
Grade 4	Discontinue infigratinib
Anemia	
Grade 3 (hemoglobin <8.0 g/dL [<4.9 mmol/L; <80 g/L]; transfusion indicated)	Hold dose of infigratinib until resolved or corrected to CTCAE Grade ≤1 or baseline, then maintain dose level
Grade 4	Hold dose of infigratinib until resolved or corrected to CTCAE Grade ≤1 or baseline, then ↓ 1 dose level
Platelet Count Decreased (Thrombocytopenia)	
Grade 3 (platelet <50,000-25,000/mm^3 [<50-25 × 10^9/L])	Hold dose of infigratinib until resolved to CTCAE Grade ≤1 or baseline, then • If resolved within ≤7 days, maintain dose level of infigratinib • If resolved between >7 days and 14 days, ↓ 1 dose level of infigratinib • If not resolved within ≤14 days, discontinue infigratinib
Grade 4 (platelet <25,000/mm^3 [<25 × 10^9/L])	• Hold dose of infigratinib until resolved to CTCAE Grade ≤1 or baseline, then ↓ 1 dose level • If not resolved within ≤14 days, discontinue infigratinib

Worst Toxicity CTCAE[a] (v5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
INVESTIGATIONS – RENAL	
Serum Creatinine	
Creatinine clearance <45 mL/min (calculated or measured)	Hold dose of infigratinib until creatinine clearance is ≥45 mL/min regardless of grade.
Serum creatinine increase Grade 2 (≥1.5-3.0 × ULN or 1.5-3.0 × baseline)	Hold dose of infigratinib until resolved to Grade ≤1 or baseline, then • If resolved within ≤7 days, maintain dose level of infigratinib • If resolved between >7 days and 14 days, ↓ 1 dose level of infigratinib • If not resolved within ≤14 days, discontinue infigratinib
Serum creatinine increase Grade ≥2	If serum creatinine CTCAE Grade ≥2 has been demonstrated in conjunction with hyperphosphatemia, serum creatinine levels must be repeated at least weekly until resolution. 24-hour urine collection should be obtained as clinically indicated for total phosphate, calcium, protein, and creatinine clearance. Ultrasound examination of the kidneys should be performed as indicated to evaluate de-novo calcifications until resolution or stabilization of creatinine.
Serum creatinine increase Grade ≥3 (>3.0 × ULN or >3 × baseline)	Discontinue infigratinib
INVESTIGATIONS – HEPATIC	
Blood bilirubin increase (For subjects with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only)	
Grade 2 (bilirubin >1.5-3.0 × ULN if baseline was normal; >1.5-3.0 × baseline if baseline was abnormal)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, then • If resolved within ≤7 days, maintain dose level of infigratinib. • If not resolved within ≤7 days, ↓ 1 dose level of study drug
Grade ≥3 (bilirubin >3.0 × ULN if baseline was normal; >3.0 × baseline if baseline was abnormal)	Discontinue infigratinib. Note: If CTCAE Grade 3 or 4 hyperbilirubinemia is due to hemolysis, then ↓ 1 dose level of infigratinib and continue treatment at the discretion of the investigator.
AST or ALT Increase	
Grade 3 (>5.0-20.0 × ULN if baseline was normal; >5.0-20.0 × baseline if baseline was abnormal)	Hold dose of infigratinib until resolved to CTCAE Grade ≤1 or baseline, then • If resolved within ≤7 days ↓, 1 dose level of infigratinib • If not resolved within ≤7 days, discontinue infigratinib
Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue infigratinib

Worst Toxicity CTCAE[a] (v5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
AST or ALT and Bilirubin Increase	
AST or ALT >3.0 – 5.0 × ULN and total bilirubin >2.0 × ULN without liver metastasis or evidence of disease progression in the liver	Hold dose of infigratinib until both transaminases and bilirubin resolved to CTCAE Grade ≤1 or baseline, then • If resolved within ≤7 days, ↓ 1 dose level of infigratinib • If not resolved within ≤7 days, discontinue infigratinib
AST or ALT >5.0 × ULN and total bilirubin >2.0 × ULN	Discontinue infigratinib
LABORATORY / METABOLIC DISORDERS	
Amylase and/or Lipase Increase	
General Comment:	A CT scan or other imaging study to assess the pancreas, liver, and gallbladder should be performed as clinically indicated within 1 week of the first occurrence of any CTCAE Grade ≥3 amylase and/or lipase.
Grade 3 (amylase or lipase >2.0 - 5.0 × ULN with signs or symptoms; >5.0 × ULN and asymptomatic)	Hold dose of infigratinib until resolved to CTCAE Grade ≤2, then • ↓ 1 dose level of infigratinib • If not resolved within ≤14 days, discontinue infigratinib For recurrent Grade 3 asymptomatic lipase or amylase elevation despite dose reduction, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤Grade 2.
Grade 4 (amylase or lipase >5.0 × ULN and with signs or symptoms)	For any Grade 4 lipase or amylase elevation, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤Grade 2.
Hypophosphatemia	
Serum phosphate <LLN-2.0 mg/dL (0.6 mmol/L)	Maintain dose level of infigratinib; decrease or hold dose of phosphate binder and optimize standard diet or medical therapy as clinically indicated to increase phosphate level.
Serum phosphate <2.0-1.0 mg/dL (<0.6-0.3 mmol/L)	Hold dose of infigratinib until resolved to >2.0 mg/dL (>0.6 mmol/L), then • ↓ 1 dose level of infigratinib. • If not resolved within ≤14 days, discontinue infigratinib.
Serum phosphate <1.0 mg/dL (<0.3 mmol/L) (life threatening consequences)	Discontinue infigratinib.
Hyperphosphatemia	
General Comment:	Optimize dose and schedule of phosphate lowering therapy in accordance with the package insert, or local or institutional guidelines
Serum phosphate >5.5–≤7.5 mg/dL	Maintain dose level of infigratinib and optimize phosphate lowering therapy as clinically indicated

Worst Toxicity CTCAE[a] (v5.0) Grade (Unless Otherwise Specified)	Dose Modifications any Time During a Cycle of Therapy
Serum phosphate >7.5 mg/dL for more than 7 days despite maximal phosphate-lowering therapy	• Hold dose of infigratinib until resolved to serum phosphate ≤5.5 mg/dL. • Restart infigratinib at the same dose level with maximal phosphate binder dosing if the subject did not receive maximal phosphate binder dosing for serum phosphate >7.5 mg/dL for >7 days.
Or, single serum phosphate >9.0 mg/dL regardless of duration or dose of phosphate lowering therapy	• Reduce one dose level of infigratinib if the subject had received maximal phosphate lowering therapy for serum phosphate >7.5 mg/dL for >7 days or if subject had a one-time serum phosphate of >9.0 mg/dL. Restart infigratinib with maximal phosphate binder dosing. It is recommended that phosphate binder dosing continues during infigratinib dose interruptions for hyperphosphatemia and that serum phosphate values be monitored frequently, eg, every 2-3 days. Phosphate binder dosing should be held during the week off infigratinib therapy each cycle (Days 22-28) unless serum phosphate is not normalized and during infigratinib dose interruptions for non-hyperphosphatemia AEs.
Serum phosphate with life-threatening consequences; urgent intervention indicated (eg, dialysis)	• Discontinue infigratinib
Hypercalcemia	
Serum calcium Grade 2 Corrected serum calcium (>11.5-12.5 mg/dL [>2.9-3.1 mmol/L]) Ionized calcium (>1.5-1.6 mmol/L), symptomatic	Hold dose of infigratinib until resolved to Grade 1 or baseline, then • If resolved within ≤7 days after suspending infigratinib, maintain dose level • If resolved between >7 days and 14 days, ↓ 1 dose level • If not resolved within ≤14 days, discontinue infigratinib
Serum calcium Grade ≥3 Corrected serum calcium (>12.5 mg/dL [>3.1 mmol/L]) Ionized calcium (>1.6 mmol/L), hospitalization indicated	Discontinue infigratinib
GASTROINTESTINAL SYSTEM DISORDERS	
Pancreatitis	
Grade 2 (asymptomatic enzyme elevation with radiologic findings only)	Hold dose of infigratinib until resolved to CTCAE Grade <2, then • ↓ 1 dose level of infigratinib • If not resolved within ≤14 days, discontinue infigratinib For recurrent Grade 2 asymptomatic radiologic pancreatitis despite dose reduction, discontinue infigratinib.
Grade 3 or Grade 4	Discontinue infigratinib

Worst Toxicity CTCAE[a] (v5.0) Grade (Unless Otherwise Specified)	Dose Modifications any Time During a Cycle of Therapy
Diarrhea	
General Comment:	Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.
Grade 1 (increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline)	Maintain dose level of infigratinib, initiate anti-diarrheal treatment
Grade 2 (increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living [ADL])	• Hold dose of infigratinib until resolved to CTCAE Grade ≤1 • Optimize anti-diarrheal treatment • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of infigratinib until resolved to CTCAE Grade ≤1, then ↓ infigratinib by 1 dose level
Grade 3 (increase of ≥7 stools/day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL)	• Hold dose of infigratinib until resolved to CTCAE Grade ≤1 • Optimize anti-diarrheal treatment • ↓ infigratinib by 1 dose level • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal antidiarrheal treatment, discontinue infigratinib
Grade 4	Discontinue infigratinib
Vomiting	
Grade 2 (outpatient IV hydration; medical intervention indicated) not controlled by optimal anti-emetic therapy	Hold dose of infigratinib until ≤Grade 1, then ↓ 1 dose level • If not resolved within ≤14 days, discontinue infigratinib
Grade 3 (tube feeding, TPN, or hospitalization indicated) not controlled by optimal anti-emetic therapy or Grade 4	Discontinue infigratinib
EYE DISORDERS (CONFIRMED BY OPHTHALMIC EXAMINATION)	
Retinal Disorders	
Grade 2 or 3 central serous retinopathy and central serous retinopathy-like events	Hold dose of infigratinib until resolved to ≤Grade 1 and continue ophthalmic evaluations • If resolved within ≤14 days, ↓ infigratinib by 1 dose level • If not resolved within ≤14 days, discontinue infigratinib
Grade ≥1 retinal vein occlusion, Grade 4 central serous retinopathy and central serous retinopathy-like events	Discontinue infigratinib

Worst Toxicity CTCAE[a] (v5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
Other Ocular/Visual Toxicity	
Grade ≥3	Hold dose of infigratinib until resolution to ≤Grade 1 • If resolution within ≤14 days, ↓ 1 dose level • If not resolved within ≤14 days, discontinue infigratinib
OTHER CLINICALLY SIGNIFICANT AEs	
Grade 3	Hold dose of infigratinib until resolved to CTCAE Grade ≤1, then ↓ 1 dose level of infigratinib • If not resolved within ≤14 days, discontinue infigratinib
Grade 4	Discontinue infigratinib

Abbreviations: ADL, activities of daily living; AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; QT, measure of time between the start of the Q wave and the end of the T wave (QT interval) in the heart's electrical cycle; QTc, QT interval corrected for heart rate; QTcF, QTc corrected by Fridericia's formula; ULN, upper limit of normal.

a CTCAE (v5.0) general guidelines:
Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

NOTE: All dose modifications should be based on the worst preceding toxicity. Subjects may have a third dose reduction only with prospective approval of a sponsor medical monitor.

7.2.5.2 Follow-up for Toxicities

Subjects whose infigratinib treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Clinical experts or specialists, such as an ophthalmologist, endocrinologist, or dermatologist, should be consulted as deemed necessary. Further guidelines and dose modifications for the management of specific infigratinib-induced toxicities (hyperphosphatemia, diarrhea) are provided in Table 7. All subjects must be followed up for AEs and SAEs for 30 days following last dose of infigratinib.

7.2.6 Anticipated Risks and Safety Concerns for Infigratinib

Eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Guidelines for prophylactic or supportive treatment for expected toxicities, including management of infigratinib-induced AEs (eg, hyperphosphatemia, renal toxicities) are provided in Table 7 and Section 7.6.1. For more information, refer to the nonclinical toxicity and/or clinical data presented in the infigratinib Investigator's Brochure.

Treatment of adverse events or laboratory abnormalities should follow the protocol where specified. If not specified in the protocol, treatment of AEs or laboratory abnormalities should be according to local institutional guidelines.

7.3 Information on Gemcitabine with Cisplatin

The active comparator in this study, gemcitabine with cisplatin, will be obtained locally by the study centers or provided centrally by the sponsor, depending on local country operational or regulatory requirements. Drug product will be stored according to the product labels.

For any commercially available product provided by the study center, every attempt will be made to source these supplies from a single lot/batch number. The study center is responsible to record the lot number, manufacturer, and expiry date for any locally purchased product as according to local guidelines, unless instructed otherwise by the sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of treatments in accordance with the protocol and any applicable laws and regulations.

Intravenous infusions of gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) will be administered according to each country's respective labeling and/or local institutional practices.

It is recommended to have cisplatin infused over 1 hour in 1000 mL of 0.9% saline containing 20 mmol potassium chloride and 8 mmol magnesium sulfate, followed by 500 mL of 0.9% saline over an additional 30 minutes before initiation of the gemcitabine infusion. The cisplatin infusion should be performed with adequate hydration according to the institution's practice. After cisplatin administration, gemcitabine, diluted in 0.9% saline according to local labeling, will be infused over approximately 30 minutes (Valle et al 2010).

The gemcitabine and cisplatin infusions will be administered on Days 1 and 8 of each 21-day treatment cycle. If one or more toxicities result in delay of cycle start, the cycle will be considered to start on the first day when any chemotherapy is administered. Subjects who cannot start a cycle within 21 days of the scheduled Day 1 (ie, within 42 days of the previous cycle Day 1) must permanently discontinue all chemotherapy unless prospectively approved by the sponsor medical monitor. If Day 8 dosing can't be given by Day 15 of a 21-day cycle, the subject should skip the Day 8 dose and dosing will resume on Day 1 of the next scheduled cycle.

Management of AEs including gemcitabine and/or cisplatin dose modification and supportive therapy (ie, growth factor administration) should follow the respective gemcitabine or local cisplatin labels and institutional guidelines.

Additional laboratory testing (not specified in the protocol), including pregnancy testing and audiometry, for either surveillance or emerging AEs should be done according to the local gemcitabine or cisplatin label and institutional standard practice.

Table 8 presents dose reduction guidelines for gemcitabine and cisplatin for neutropenia and/or thrombocytopenia.

If a subject cannot tolerate cisplatin, they can remain on gemcitabine alone. However, if gemcitabine is discontinued due to toxicity then all study treatment must be discontinued. The subject will have an EOT visit and then continue on study for PFS, PFS2, and OS follow-up (even if the subject starts new anticancer treatment).

Table 8: Dose Reduction/Interruption Guidelines for Gemcitabine and Cisplatin

Neutrophils ($\times 10^6$/L)		**Platelet Count ($\times 10^6$/L)**	**% of Full Dose (Gemcitabine)**	**% of Full Dose (Cisplatin)**
≥1000 (≥1.0×10^9/L)	And	≥100,000 (≥100×10^9/L)	100	100
500-999 (0.50-0.99×10^9/L)	Or	50,000-99,000 (50-99×10^9/L)	75	100
<500 (<0.50×10^9/L)	Or	<50,000 (<50×10^9/L)	Hold	Hold

General guidelines for non-hematologic toxicity for gemcitabine include:

- Hold or decrease gemcitabine dose by 50% for the following: severe (Grade 3 or 4) non-hematologic toxicity until resolved (excludes nausea, vomiting, or alopecia [no dose modifications recommended])

- Permanently discontinue gemcitabine for any of the following: unexplained dyspnea (or other evidence of severe pulmonary toxicity), severe hepatotoxicity, hemolytic uremic syndrome, capillary leak syndrome, posterior reversible encephalopathy syndrome

Subjects should be monitored for signs of dehydration, kidney function, ototoxicity, neuropathy and hypersensitivity reaction with cisplatin administration, and adjust cisplatin treatment according to local labeling and institution standard.

Subjects whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Clinical experts or specialists should be consulted as deemed necessary. All subjects must be followed up for AEs and SAEs for 30 days following last dose of study drug.

7.4 Randomization

Subjects will be randomized in a 2:1 ratio to one of the two treatment groups. Randomization should occur within 5 days before Cycle 1 Day 1. Randomization will be stratified by unresectable locally advanced vs metastatic disease, geographic region (North America, Western Europe, Asia Pacific, and rest of the world), prior neoadjuvant/adjuvant treatment (yes/no), and received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no). Documented medical monitor approval is required prior to randomization. Interactive Response Technology will be used to assign subjects to treatment based on the randomization stratification factors entered into the system. Site personnel will be given a unique subject number for each subject, consisting of a unique center number followed by a sequential subject number suffixed to it.

This is an open-label study; all study drugs will be administered in an open label fashion.

7.5 Compliance

The investigator or responsible site personnel should instruct the subject to take infigratinib exactly as prescribed to promote compliance. All dosages prescribed and dispensed to the subject and all dose changes or missed doses during the study must be recorded on the appropriate eCRF as outlined in the Case Report Completion Guidelines. Subject re-training for infigratinib dosing non-compliance should be conducted and documented, as needed.

For subjects in the gemcitabine plus cisplatin group, administration of study drugs will be captured in the appropriate eCRF and source documents.

7.6 Supportive Care Guidelines

7.6.1 Infigratinib Group

Any palliative and supportive care for disease related symptoms, including any medication or therapy for a concurrent medical condition are permitted, except if specifically prohibited below.

Hematopoietic Growth Factors

Hematopoietic growth factors (eg, erythropoietin [EPO], granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor [GM-CSF]) and blood transfusions are not to be administered prophylactically or to be used to meet eligibility criteria. However, these drugs may be administered as according to the label of these agents or as dictated by local practice or guidelines established by the American Society of Clinical Oncology (ASCO), ESMO, or other appropriate regional societies.

Management of Hyperphosphatemia

Hyperphosphatemia is a recognized on-target effect of potent and selective inhibitors of the FGFR pathway. While on infigratinib, subjects should avoid foods that are especially high in phosphate and, if possible, should restrict dietary phosphate to 600 – 800 mg/day. High-phosphate foods include dairy products; meats, nuts, and other high-protein foods; processed foods; and dark colas.

Subjects who have experienced hyperphosphatemia should take a phosphate binder such as sevelamer, sucroferric oxyhydroxide, lanthanum carbonate, ferric citrate, etc. within 30 minutes of a meal on the day while taking infigratinib. Once the subject has had hyperphosphatemia, the subject should remain on a low phosphate diet, if possible, and take phosphate binder on the days infigratinib is taken, even if the serum phosphate is normalized. Unless otherwise specified by the local prescribing information or institutional practice, the following regimen should be used to manage hyperphosphatemia:

- For serum phosphate >5.5 – <7.5 mg/dL
  - Start sevelamer 800 mg three times a day with meals
  - Increase the dose of sevelamer up to 1200 mg every 8 hours
- For serum phosphate ≥7.5 mg/dL
  - Increase the dose of sevelamer up to 1600 mg (2 tablets per meal) every 8 hours
  - Consider adding acetazolamide two to three 250 mg tablets per day.

During the infigratinib cycle, subjects do not need to be on a low phosphate diet or take a phosphate binder during their 1-week off period unless serum phosphate is not normalized. Other dose modification recommendations are provided in Table 7, but should be modified according to country or institutional practice.

Management of Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/anti-motility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, infigratinib should be temporarily interrupted or dose reduced according to Table 7.

Management of Bone Metastatic Disease

Treatment of bone metastatic disease with symptomatic standard of care therapy according to institutional guidelines, including prophylactic treatment with bisphosphonates, palliative localized radiation therapy, and symptomatic treatment with steroids and pain medications is allowed. Initiation of other systemic anticancer therapy as described in Section 7.7.1.2 is not allowed and requires permanent discontinuation of study treatment.

Management of Alopecia, Palmar-Plantar Erythrodysesthesia, Paronychia, and Stomatitis

Recommendations for management (not required per protocol) of alopecia, palmar-plantar erythrodysesthesia syndrome, paronychia (adapted from Segaert 2005), and stomatitis (adapted from Rugo et al 2017) are provided in Table 9. These are guidelines only and institutional guidelines should be followed where applicable.

Table 9: Recommendations for Management of Alopecia, Palmar-Plantar Erythrodysesthesia Syndrome, Paronychia, and Stomatitis

Alopecia	
Grade 1	Continue study drug • Minoxidil 5% (OTC) solution or foam once daily to scalp
Grade 2	Continue study drug • Minoxidil 5% (OTC) solution or foam twice daily to scalp • Fluocinonide 0.05% solution daily to scalp
Palmar-plantar erythrodysesthesia syndrome	
Grade 1	Continue study drug • Urea 20% or ammonium lactate 12% lotions BID to hands and feet
Grade 2	Continue study drug • Urea 20% or ammonium lactate 12% BID to hands and feet • Fluocinonide 0.05% cream BID to hands and feet
Grade 3	Hold study drug until resolved to Grade ≤1 • Urea 20% or ammonium lactate 12% BID to hands and feet • Fluocinonide 0.05% cream BID to hands and feet
Paronychia	
Grade 1	Continue study drug • Clindamycin 1% solution around and under nails TID • Soak for 15 minutes daily in white vinegar in tap water (1:1)
Grade 2	Continue study drug • Obtain bacterial cultures to confirm sensitivity to antimicrobial • Cefadroxil 500 mg BID or TMP/SMX DS BID for 14 days • Soak for 15 minutes daily in white vinegar in tap water (1:1) • Dermatology consultation
Grade 3	Hold study drug until resolved to Grade ≤1 • Obtain bacterial cultures to confirm sensitivity to antimicrobial • Cefadroxil 500 mg BID or TMP/SMX DS BID for 14 days • Dermatology consultation
Stomatitis	
Grade 1/2	Continue study drug • Dexamethasone elixir 0.5 mg/5 mL swish and spit 1 teaspoon (5mL) TID.
Grade 3	Hold study drug until resolved to Grade ≤1 • Dexamethasone elixir 0.5 mg/5 mL swish and spit 1 teaspoon (5 mL) TID. • Clotrimazole 10 mg lozenges 3-5 times/day

BID=2 times daily; OTC=over-the-counter; TID=3 times daily; TMP/SMX DS=sulfamethoxazole and trimethoprim

7.6.2 Gemcitabine with Cisplatin Group

Subjects in the gemcitabine with cisplatin group can receive any palliative and supportive care for disease related symptoms, as clinically indicated and in accordance with standard of care.

Cisplatin is associated with a high emetic potential; anti-emetics are recommended to prevent nausea and vomiting.

Hematopoietic growth factors (eg, EPO, G-CSF, GM-CSF) and blood transfusions are not to be used to meet eligibility criteria. However, these drugs may be administered as according to the label of these agents or as dictated by local practice or guidelines established by the ASCO, ESMO, or other appropriate regional societies.

7.7 Prior and Concomitant Medications

At Screening, subjects are to be asked about their history of prior therapies (including prior anticancer therapy); investigators are to check for use of any disallowed prior medications, as outlined in the exclusion criteria for the study (Section 6.2).

Live vaccines are prohibited within 30 days before the first dose of study drug, for the duration of study participation, and for a period of time (approximately 3-6 months) after the last dose of chemotherapy according to local guidelines.

For each subject enrolled in the study, all anticancer therapies ever taken for cholangiocarcinoma and other medications taken within 28 days of first dose of study drug are to be recorded on the appropriate page of the eCRF.

All prescription and non-prescription medications administered from the time of first dose of study drug through 30 days after last dose are to be recorded for each subject on the appropriate page of the eCRF. Dates for the start and stop of each concomitant medication are to be recorded, as well as the reason for administration (particularly if administered for an AE). Any changes in dose of concomitant medications are to also be recorded.

Cancer medications taken by the subject after last dose of study drug are to be recorded on the Post Study Anticancer Medications page of the eCRF, and non-medication cancer therapies and surgeries are to be recorded on the Post Anticancer Therapies page of the eCRF.

Hormone replacement therapies such as thyroid and growth hormones are allowed, as well as estrogen replacement hormone treatment.

7.7.1 Infigratinib Group

7.7.1.1 Permitted Concomitant Therapy Requiring Caution and/or Action

Details for specific medications which require action and/or caution while on study in subjects taking infigratinib are provided in Appendix 1 (Section 17.1). The rationale for these medications is provided below.

Infigratinib is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper GI tract may alter the solubility of infigratinib, and limit bioavailability. These agents include, but are not limited to, proton pump inhibitors (eg, omeprazole), H2-antagonists (eg, ranitidine) and antacids. Proton pump inhibitors are prohibited due to their long PD effect and should be replaced with H2-antagonists or

antacids. Infigratinib should be taken ≥2 hours before or 10 hours after dosing with H2-antagonists. Antacids, locally acting acid neutralizing agents, are to be separated from infigratinib doses by 2 hours.

Infigratinib is a substrate of CYP3A4. If anticoagulation is required, heparin and/or low-molecular-weight heparins or direct thrombin inhibitors and/or Factor Xa inhibitors that are not metabolized by CYP3A4 (eg, dabigatran, edoxaban) are to be used. Anticoagulants that are CYP3A4 substrates and have a narrow therapeutic index (eg, warfarin sodium or any other coumadin-derivative anticoagulants or certain direct thrombin inhibitors [eg, argatroban] or Factor Xa inhibitors [eg, rivaroxaban]) should be used with caution. Refer to Section 7.7.1.2 for further information on CYP3A4.

Infigratinib was shown in vitro to inhibit the drug transporter breast cancer resistance protein (BCRP), with an IC_{50} of 210 nM. While the clinical relevance of this inhibition is unknown, drugs transported by BCRP should be used with caution.

Anti-emetics are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines, with the following considerations:

- Ondansetron has a known risk for Torsade de Pointes, and therefore should be used with caution. Palonosetron may be used as an alternative.

- Aprepitant (brand name: Emend) is both a sensitive substrate and a moderate CYP3A4 inhibitor and is prohibited with infigratinib. Similarly, the use of other agents in the neurokinin-1 (NK-1) receptor antagonist class (casopitant and fosaprepitant) is limited by drug interactions and is prohibited with infigratinib.

It is recommended to avoid using drugs that are known to cause QT prolongation. See Appendix 1 (Section 17.1) for list of drugs that need to be used with caution.

Preliminary clinical data have shown that infigratinib has no effect on cardiac conduction or ECG intervals (see current version of the infigratinib Investigator's Brochure). However, medications that have the potential to prolong the QT/QTc interval or induce Torsade de Pointes (possible and conditional risk of TdP/QT prolongation) are allowed with caution. Investigators at their discretion may co-administer such medications, but subjects should be carefully monitored. See Appendix 1 (Section 17.1) for list of drugs that need to be used with caution. Please note that the list might not be comprehensive.

7.7.1.2 Prohibited Concomitant Therapy

A concomitant medication is considered prohibited if it appears on any of the prohibited medication lists for any clinical pharmacology property of the drug (eg, CYP, BCRP).

Details for specific medications prohibited while on study are provided in Appendix 2 (Section 17.2). The rationale for the restricted medications is provided below.

Other investigational therapies must not be used while the subject is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study drug must not be given to subjects while the subject is on study drug. If such agents are required, then the subject must be discontinued from study drug. The only exception is palliative localized radiation therapy for bone metastases with approval by the sponsor medical monitor.

Proton pump inhibitors are prohibited; see Section 7.7.1.1 for rationale.

Infigratinib is a substrate of CYP3A4. Therefore, strong and moderate inhibitors and inducers should be avoided. Strong and moderate inhibitors of CYP3A4 such as the ones listed in Appendix 2 (Section 17.2) are prohibited because infigratinib is a likely substrate of this isoenzyme; these include the anti-emetic aprepitant (brand name: Emend) and other agents in the NK-1 receptor antagonist class (casopitant and fosaprepitant), as described in Section 7.7.1.1. Strong inducers of CYP3A4 are prohibited because their usage may decrease the exposure of infigratinib. Therefore, agents such as those listed in Appendix 2 (Section 17.2) are prohibited. Please note that the list may not be exhaustive.

Subjects in the infigratinib group must also avoid the consumption of grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or juice within 7 days prior to the first dose of infigratinib and throughout the treatment period due to a potential CYP3A4 interaction with study drug.

Medications that increase the serum levels of phosphate and/or calcium are prohibited.

7.7.2 Gemcitabine with Cisplatin Group

Subjects in the gemcitabine with cisplatin group cannot receive any investigational therapies while the subject is on gemcitabine and cisplatin. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than study drug (gemcitabine with cisplatin) must not be given to subjects while the subject is on study drug. If such agents are required, then the subject must be discontinued from study drug. The only exception is palliative localized radiation therapy for bone metastases with approval by the sponsor medical monitor.

Antiemetic therapy, including premedications prior to chemotherapy, and anti-diarrheal medications can be used as clinically indicated and in accordance with standard of care.

7.7.3 COVID-19 Vaccinations

The effect of COVID-19 vaccines has not been studied in combination with infigratinib; hence the safety and efficacy of either agent when used in combination are unknown (ie, vaccination before, during, or after infigratinib treatment has not been studied, and the efficacy and safety of COVID-19 vaccines in the presence of infigratinib, as well as the efficacy and safety of infigratinib in the presence of a COVID-19 vaccine, are unknown). Similarly, the safety and efficacy of combining COVID-19 vaccinations with gemcitabine and cisplatin are unknown.

There is no detailed or conclusive information on studies conducted with the COVID-19 vaccines in patients receiving any anticancer therapies, or in patients with cancer. In general, COVID-19 vaccines may be administered before, during, and after study participation, if determined to be safe in the clinical judgement of the treating physician/study investigator. The treating physician/study investigator should assess the risk for each individual study subject for receiving the vaccine in the context of the study.

Whenever feasible, vaccinations should be administered at least 30 days prior to randomization. Live vaccines are prohibited as specified in Section 7.7.

All applicable guidelines should be followed, and vaccinations should adhere to the manufacturer's guidelines for eligibility and contraindications to receive the vaccine (ASCO 2021; Garassino 2020; Pergam 2021). Subjects vaccinated for COVID-19 should be closely monitored, and any observed AEs/SAEs should be reported as outlined in Section 10.5.1.

7.8 Non-drug Therapies

Any significant non-drug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered from the time of first dose of study drug through 30 days after last dose are to be recorded for each subject on the appropriate page of the eCRF. Dates for the start and stop of each therapy are to be recorded, as well as the reason for administration (particularly if administered for an AE).

Non-drug therapies are prohibited if they appear on any of the prohibited medication lists for any clinical pharmacology or PK property of the drug (eg, CYP, BCRP) (see Appendix 2 [Section 17.2]).

8 SUBJECT DISCONTINUATION AND STUDY TERMINATION

8.1 Subject Discontinuation

8.1.1 Discontinuation of Study Drug

In rare instances, it may be necessary for a subject to permanently discontinue study treatment. If study treatment is permanently discontinued, the subject will remain in the study to be evaluated for safety follow-up and follow-up of disease progression and survival status. See Section 2 for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

Subjects must be discontinued from study drug for:

- Radiographic PD confirmed by BICR.
- Pregnancy
- AE that leads to substantial changes in individual risk-benefit considerations

- Dose delay of >14 days for infigratinib or >21 days for chemotherapy, with exceptions noted in Section 7.2.5.1 and Section 7.3, respectively, and approval by the sponsor medical monitor.

- Death

In addition, subjects may be discontinued from study drug for any of the following reasons:

- Treatment phase complete (gemcitabine plus cisplatin arm)

- New medical condition that does not allow continuation of study drug compliance

- Protocol deviation, including non-compliance with dosing regimen

- Lost to follow-up (defined as no contact after 3 documented attempts by telephone followed by 1 attempt via letter [eg, certified mail, if available])

- Subject request

- Investigator request

- Central finding does not confirm FGFR2 fusion or rearrangement and the investigator elects to discontinue study treatment (subjects in the infigratinib arm)

- Subject is found to be MSI-H and the investigator elects to discontinue study treatment.

  Of note: postrandomization, if the subject is determined to be MSI-high and/or does not have FGFR2 fusion or rearrangement confirmed by molecular testing by the central laboratory, the subject may continue on study treatment. This requires a joint decision by the subject and investigator and documentation of subject consent to continue on study treatment.

If a subject is discontinued from study drug, the investigator is to notify the sponsor. At the time of discontinuation of study drug, subjects are to complete the EOT visit, followed 30 days later by the 30-day Follow-up visit. Thereafter, subjects will be followed for disease progression and survival (as previously described). Subjects who discontinue study drug for reasons other than PD confirmed by BICR will continue to have radiographic assessments every 8 weeks ±7 days until radiographic PD confirmed by BICR.

The reason for discontinuation of study drug is to be documented in the eCRF. Further, if a subject is withdrawn from treatment due to protocol deviation or investigator's request, specifics are to be recorded in the eCRF.

8.1.2 Discontinuation from Study

Subjects have the right to withdraw from the study at any time and their request without prejudice or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon. At the time of discontinuing from the study, if possible, an EOT visit should be conducted, as shown in Section 2. See Section 2 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Subjects may be discontinued from the study for the following reasons:

- Subject's formal withdrawal of informed consent:
    - If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
    - If a subject withdraws from the study, the subject may request destruction of any samples taken and not tested, and the investigator must document this in the study records and notify the sponsor immediately.
- Investigator request
- Lost to follow-up (defined as no contact after 3 documented attempts by telephone followed by 1 attempt via certified letter)
- Discontinuation of the study by the sponsor
- Protocol deviation
- Study complete
- Death
- Other

The reason for discontinuation from the study is to be documented in the eCRF. The investigator should make every effort to determine why a subject is lost to follow-up or withdraws consent and record this information in the eCRF. Further, if a subject is withdrawn due to protocol deviation or investigator's request, specifics are to be recorded in the eCRF.

8.2 Study Termination

The study can be terminated at any time for any reason by the sponsor. Should this be necessary, every effort is to be made to ensure that the subject completes certain assessments, depending on where they are in the study. If a subject is still on study drug,

the subject is to complete the EOT visit. If the subject has already discontinued study drug, he/she is to complete the 30-day Safety follow-up visit (if not already completed). EOS reasons will be recorded for all subjects.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the early termination of the trial.

9 STUDY VISITS AND PROCEDURES

See Section 2 for the Schedules of Assessments (Table 2, Table 3, Table 4, and Table 5).

9.1 Molecular Prescreening

The sponsor must review and approve local tests for FGFR2 status to determine that the local laboratory result complies with the study protocol and definition of a known or likely activating FGFR2 fusion/rearrangement (refer to Section 10.3.1). If the FGFR2 fusion/rearrangement status from a local test performed on tumor tissue that is compliant with local requirements for laboratory-developed tests or in vitro diagnostic devices (IVDs) is not available, molecular prescreening is required to confirm the presence of FGFR2 fusion/rearrangement from tumor tissue. If archival tumor tissue is available with a pathology report, molecular prescreening will be done using this sample. Otherwise, newly obtained tumor tissue collected before randomization will be required. The archival or newly obtained tumor tissue will be sent to a sponsor-designated central laboratory. Results of the analysis will be communicated to each respective study center.

For China, all molecular prescreening will be performed by the contracted laboratory in China to determine the FGFR2 status.

If FGFR2 data are not available prior to consent and molecular prescreening is required, subjects must provide written informed consent for molecular prescreening (Section 13.3). Molecular prescreening assessments can be done any time prior to the initiation of screening for the study.

For subjects who sign the prescreening informed consent form (ICF), AEs which occur after signature of this consent and prior to signing the main informed consent will be captured if they meet the definition of serious and are reported to be causally related with study procedures (eg, an invasive procedure such as biopsy) (Section 10.5.1.3).

For all subjects undergoing molecular prescreening, data collected as part of the assessment for FGFR2 fusion/rearrangement, including the following, will be collected and used for analysis of the exploratory objectives: (1) other genetic alterations identified on the F1CDx gene panel as well as tumor mutational burden, and microsatellite instability (MSI); (2) primary tumor site; (3) anatomic site of specimen collection (specimen site) and date of sample collection; (4) disease diagnosis; (5) specimen type

(FFPE block or FFPE slides); (6) gender; (7) age at the time of informed consent; and (8) country.

9.2 Main Informed Consent

The subject will sign the main study ICF to begin screening procedures (Section 13.3). Informed consent must be obtained before conducting any study-specific procedures. A copy of the ICF must be given to the subject or to the person signing the form. The investigator or designee must record the date when the study informed consent was signed in the medical records of the subject.

9.3 Screening (Day −28 to −1)

After the main ICF is signed, screening activities will include the following:

- Collection of written documentation of local or central laboratory determination of known or likely activating FGFR2 fusions/rearrangements (see Section 9.1). Note: Central confirmation is not required prior to enrollment in study. Subjects with/without central confirmation of FGFR2 fusions/rearrangements are expected to follow the same study procedures.
- Demography
- I/E criteria assessment
- ECOG performance status
- Relevant medical history/current medical conditions
- Diagnosis, primary location, and extent of cancer
- Prior anticancer therapy
- Height and weight
- AEs (see Section 10.5.1.3)
- Prior medication use
- Physical examination
- Vital signs
- Ophthalmic assessment (performed by an ophthalmologist)
- Blood draw for hematology, chemistry, and coagulation assessment

  - To calculate calcium-phosphorus product (as noted in Exclusion Criterion #16): multiply the serum value of calcium in mg/dL by the serum phosphate in mg/dL. The calcium level used for this calculation and assessment of whether the subject has an abnormal calcium level should be corrected for serum albumin (Block 2004; Young 2004; Young 2005).

- Urinalysis (micro- and macroscopic)
- Pregnancy test (blood or urine) for WOCBP
- 12-lead ECG
- Computed tomography (CT)/ magnetic resonance imaging (MRI) scans (chest, abdomen, and pelvis), unless available within 28 days prior to randomization (for subjects who receive up to 1 cycle of gemcitabine-based chemotherapy before randomization, the baseline imaging assessment must be conducted ≥7 days after the last dose of chemotherapy and before randomization)
- Sufficient archival or newly obtained tumor sample for central confirmation of FGFR2 fusions/rearrangements by central laboratory (only if a tumor sample was not sent for central molecular prescreening) (see the Laboratory Manual for sample requirements for the central laboratory).

In the event that subjects have a baseline/screening laboratory assessment that excludes them from the study, the baseline/screening laboratory assessment can be repeated.

9.4 Treatment Period: Cycle 1 Day 1

Before the start of dosing on Cycle 1 Day 1, the following assessments are to be performed. Baseline/screening assessments that are conducted within 3 days prior to first treatment can be used to satisfy the Day 1 requirement.

- ECOG performance status
- Weight
- Prior and concomitant medication use
- Symptom-directed physical examination (if needed)
- Vital signs
- Blood draw for hematology, chemistry; blood draw for coagulation, if clinically indicated
- Blood sample for PK assessment (first 40 subjects enrolled in the infigratinib group)

- Blood sample for assessment of cell-free tumor DNA
- Urinalysis (micro- and macroscopic), if clinically indicated
- Pregnancy test (blood or urine) for WOCBP
- 12-lead ECG
- AEs (see Section 10.5.1.3)
- EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BIL21 prior to all other study procedures (and in order of EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BIL21)

Note: Audiometry should be done for subjects assigned to gemcitabine/cisplatin, as required by the cisplatin local label or standard institutional guidelines.

Subjects will then receive their first dose of infigratinib or gemcitabine plus cisplatin, depending on their treatment assignment.

For the first 40 subjects enrolled in the infigratinib group, a blood sample will be collected 4 hours (±30 minutes) after infigratinib dosing for PK analysis. A sample will also be collected on Day 2 of Cycle 1 (24 hours [±1 hour] after the Day 1 dose prior to Day 2 dosing).

Subjects in the infigratinib group will be dispensed study drug and instructed on daily dosing using a "3 weeks on, 1 week off" schedule for each 28-day treatment cycle. Subjects in the gemcitabine plus cisplatin group will be instructed to return to the study center on Day 8 to receive their next scheduled dose of study drug.

9.5 Rest of Treatment Period

Subjects will continue to receive infigratinib or gemcitabine with cisplatin, as described in Section 7.1.

During the treatment period, CT/MRI scans (chest, abdomen, and pelvis) will be taken every 8 weeks from the first dose of study drug, regardless of treatment interruption. For post-baseline imaging and ophthalmic assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted).

Blood samples for assessment of cell-free tumor DNA will be collected every 8 weeks (±1 week) at the same visit as CT/MRI scans, regardless of treatment interruption. All samples are to be collected predose on dosing days.

QOL assessments (EQ-5D, EORTC QLQ-C30, EORTC QLQ-BIL21) will be done every 4 weeks (±1week) from last assessment through Cycle 3; then every 8 weeks (±1 week), regardless of treatment interruption. These assessments should be completed on the

specified visit day prior to all other study procedures and in order of EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BIL21.

Tumor samples may be collected during the treatment period upon disease progression and will be used to explore mechanisms of disease progression. Such sample collection requires documented subject informed consent.

All subjects in the infigratinib group will have blood samples collected on Day 21 of Cycles 1 through 4 at 0 (predose) and 4 hour (±30 minutes) postdose for PK analysis.

In addition, a PK substudy will be conducted on the first 40 subjects enrolled who receive infigratinib. These subjects will have PK blood samples collected at the following time points in Cycle 1: Day 1 (0 [predose] and 4 hours [±30 minutes] postdose), Day 2 (24 hours [±1 hour] after the Day 1 dose prior to Day 2 dosing), Day 21 (0 [predose] and 4 hours [±30 min] postdose), Day 22 (24 hours [±1 hour] after the Day 21 dose) of Cycle 1, and the same as all other subjects in the infigratinib group: Day 21 of Cycles 2 through 4 at 0 (predose) and 4 hours (±30 minutes) postdose. If PK results are not evaluable for a subject, then that subject will be replaced with a subject treated with infigratinib to a total of 40 subjects enrolled in the PK substudy.

Throughout the treatment period, subjects will be monitored for AEs and concomitant medication use. Other safety assessments, including symptom-directed physical examinations; vital signs; ophthalmic assessments (performed by an ophthalmologist); laboratory measures (hematology, blood chemistry, coagulation, pregnancy) and urinalysis; and 12-lead ECG will be conducted at the times indicated in Table 2 and Table 4.

In addition, for subjects assigned to gemcitabine/cisplatin, audiometry should be done for subjects assigned to gemcitabine/cisplatin, as required by the cisplatin local label and standard institutional guidelines.

Of note, if a subject has a dose delay and cannot receive study treatment for a visit, all safety labs must be conducted on the dosing visits that are listed in the schedule of assessments (Section 2) for the intended dosing day. In the event of missed/delayed infigratinib doses, a PK blood sample should be collected if the sample can be collected within 24 hours of the last dose.

Weight will be taken, and ECOG performance status will be assessed, at the times indicated in Table 2 and Table 4.

9.6 EOT Visit

When the decision is made to discontinue study drug, subjects will complete an EOT visit, no later than 8 days from the decision to discontinue study drug.

If a subject discontinues study drug for reasons other than radiographic PD confirmed by BICR, CT/MRI scans (chest, abdomen, and pelvis) should be taken at the EOT visit, unless taken within the previous 4 weeks.

Other assessments will include the following:

- ECOG performance status
- Weight
- Concomitant medication use
- Physical examination
- Vital signs
- Ophthalmic assessment (performed by an ophthalmologist)
- Blood draw for hematology, chemistry
- Pregnancy test (blood or urine) for WOCBP
- 12-lead ECG
- EQ-5D, EORTC QLQ-C30, EORTC QLQ-BIL21 (prior to all other study procedures and in order of EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BIL21); these assessments are not required if they were completed within the previous 7 days at a regularly scheduled visit.
- AEs
- Blood sample for assessment of cell-free tumor DNA (if not done within the previous 28 days).

For any subject in the infigratinib group who permanently discontinues study drug for any reason, attempts should be made to collect a PK blood sample from the subject at the time of discontinuation, if the sample can be collected within 24 hours of last dose.

9.7 30-day Safety Follow-up Visit

All subjects must complete safety follow-up assessments 30 days after the last dose of the study drug, as outlined in Table 2 and Table 4. Information relating to anticancer therapies taken since discontinuation of study drug and AEs (including concomitant medication taken for ongoing AEs) will be collected for 30 days after the last dose of the study drug.

9.8 Follow-up of Disease Progression and Survival Status

Subjects who discontinue study drug for radiographic PD confirmed by BICR will be followed approximately every 3 months (via telephone or office visit) for survival status and new anticancer therapy information (subsequent therapy and progression/PFS2) until EOS, defined as the time when at least 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment. The following will be collected for new anticancer therapy information:

- Name(s) of new anticancer therapy regimens.
- New anticancer therapy dates of initiation and completion.
- Date of radiographic progression to the first new anticancer therapy (PFS2).
- Response to subsequent anticancer therapies and reason for discontinuation.

Subjects who discontinue study drug for reasons other than radiographic PD confirmed by BICR will continue to have radiographic assessments every 8 weeks ±7 days until radiographic PD confirmed by BICR (even if subjects start new anticancer treatment). Thereafter, these subjects will be followed approximately every 3 months for survival status and use of anticancer therapy, as described above.

At the time that PD is confirmed (by BICR and/or investigator), a blood sample will be collected for analysis of cell-free tumor DNA.

For subjects assigned to gemcitabine/cisplatin, pregnancy testing every 4 weeks for 6 months or other schedule should be done after the last infusion of gemcitabine and cisplatin if required according to the local gemcitabine or cisplatin label and local institutional practice.

9.9 Crossover to Infigratinib

Subjects randomized to the gemcitabine with cisplatin group may be eligible to cross over and receive infigratinib following radiographic PD confirmed by BICR. Before these subjects receive any infigratinib, the following exclusion criteria must be rechecked: Exclusion Criteria 4, 7-10, 13, 14, 16-18 (see Section 6.2). Assessments performed within the past 30 days may be used to check these criteria. Crossover requires approval by the medical monitor.

Subjects randomized to the gemcitabine with cisplatin group who cross over must complete their 30-day Safety Follow-up visit for gemcitabine with cisplatin before receiving any infigratinib. If a subject is receiving ondansetron, its use must be discontinued with a washout period of at least 24 hours before receiving any infigratinib.

Crossover subjects will be dispensed study drug and instructed on daily dosing using a "3 weeks on, 1 week off" schedule for each 28-day treatment cycle.

Subjects who cross over to infigratinib will continue on treatment until unacceptable toxicity or other reason listed in Section 8.1.1.

Subjects who cross over to infigratinib will be evaluated for safety, ECOG performance status, PFS2, OS and blood collection for cell-free DNA, as outlined in Table 5.

9.10 End of Study

EOS is defined as the time when 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment. At the EOS, the investigator is to document the primary reason for EOS for each subject, as defined in Section 8.1.2.

10 STUDY ASSESSMENTS

10.1 Efficacy Assessments

Efficacy will be assessed by tumor response to study drug. To assess each subject's response, CT/MRI scans will be performed.

Chest, abdomen, and pelvic CT scans are required for all subjects at screening, unless available within 28 days prior to randomization. A contrast-enhanced MRI (if possible) of the chest, abdomen, and pelvis should be performed if a subject is known to have a contraindication to IV contrast at baseline or develops a contraindication during the trial. CT/MRI of the brain should be performed if clinically indicated. Details are provided in the Subject Scanning Guide.

For subjects with skeletal lesions suspected at screening, whole-body bone imaging should be obtained either with a TC99 bone scan or alternatively a NaF CT/ MRI PET scan, with local CT of any identified lesions. Of note, the CT or MRI portion of the scan should only be substituted for the required chest, abdomen, and pelvic CT scans if the CT or MRI is of diagnostic quality and meets all requirements as described in the study imaging guide (ie, oral and IV contrast, slice thickness, and anatomic coverage). Postbaseline, if skeletal lesions are identified at screening, which are not visible on the chest, abdomen or pelvis CT/MRI scan, bone imaging with either a TC99 bone scan or NaF CT/MRI PET is required at all postbaseline imaging timepoints (every 8 weeks). In all cases that postbaseline bone imaging is required, the same modality that was used at screening should be used for all postbaseline imaging when possible.

During the treatment period, CT/MRI scans (chest, abdomen, and pelvis) will be taken every 8 weeks from the first dose of study drug, regardless of treatment interruption. For post-baseline imaging assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted).

If a subject discontinues study drug for reasons other than radiographic PD confirmed by BICR, CT/MRI scans (chest, abdomen, and pelvis) should be taken at the EOT visit, unless taken within the previous 4 weeks. Thereafter, these subjects will continue to have radiographic assessments every 8 weeks ±7 days until radiographic PD confirmed by

BICR (even if subjects start new anticancer treatment). Subjects who cross over from the gemcitabine-cisplatin group to receive infigratinib, after radiographic PD confirmed by BICR, will continue to have radiographic tumor assessments every 8 weeks for investigator assessment of efficacy.

Subjects are to be evaluated for all potential sites of tumor lesions at each assessment time point. Any lesion that has been previously treated with radiotherapy should be considered as a non-target lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a target lesion. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow-up.

Measurable disease according to RECIST v1.1 is not required for study entry (ie, a subject with non-target disease only may be enrolled into the study if they meet all other eligibility criteria). Tumor response will be evaluated by BICR and by the investigator according to RECIST Version 1.1 (Eisenhauer et al 2009). Summaries of the time point responses for target lesions (if applicable, Table 10), non-target lesions (Table 11), and overall response (Table 12) are provided below for reference.

All radiographic assessments, including imaging obtained at unscheduled time points to determine disease progression, as well as imaging obtained for other reasons but captures radiographic progression, will be sent for BICR. Refer to the Study Manual for details regarding image collection and shipment.

Once radiographic PD has been confirmed by BICR and documented, survival status and new anticancer therapy information (subsequent therapy and progression/PFS2) will be followed approximately every 3 months (via telephone or office visit) until EOS, defined as the time when at least 224 OS events have been reached (for the primary OS analysis) and the last subject has completed study treatment.

For any subject with a centrally unreadable baseline scan, PD will be considered confirmed (for study conduct purposes, not analysis) when the study center submits their local PD notification for BICR.

Table 10: Response Criteria for Target Lesions

Response criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.[a]
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

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

[a] The appearance of one or more new lesions is also considered progression.

Source: Eisenhauer et al 2009

Table 11: Response Criteria for Non-target Lesions

Response criteria	Evaluation of non-target lesions
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).
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Abbreviations: CR, complete response; PD, progressive disease.

Source: Eisenhauer et al 2009

Note: Unequivocal progression in non-target lesions must be substantial and generally sufficient to require change in therapy. The increase in overall disease burden should be 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 diameter in a measurable lesion).

Table 12: Overall Lesion Response at each Assessment

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

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

Source: Eisenhauer et al 2009

10.2 Pharmacokinetic Assessments

All subjects in the infigratinib group will have blood samples collected on Day 21 of Cycles 1 through 4 at 0 (predose) and 4 hours (±30 minutes) postdose for PK analysis (Table 2).

In addition, a PK substudy will be conducted on the first 40 subjects enrolled who receive infigratinib. These subjects will have PK blood samples collected at the following time points in Cycle 1: Day 1 (0 [predose] and 4 hours [±30 minutes] postdose), Day 2 (24 hours [±1 hour] after the Day 1 dose prior to Day 2 dosing), Day 21 (0 [predose] and 4 hours [±30 min] postdose), Day 22 (24 hours [±1 hour] after the Day 21 dose), and the same as all other subjects in the infigratinib group: Day 21 of Cycles 2 through 4 at 0 (predose) and 4 hours (±30 minutes) postdose (Table 3). If PK results are not evaluable for a subject, then that subject will be replaced with a subject treated with infigratinib to a total of 40 subjects enrolled in the PK substudy.

For any subject in the infigratinib group who permanently discontinues study drug for any reason, attempts should be made to collect a PK blood sample from the subject at the time of discontinuation, if the sample can be collected within 24 hours of last dose.

All blood samples will be taken from a central line, by direct venipuncture, or with an indwelling cannula inserted in a peripheral vein.

On the days of PK sampling, subjects should take their study drug at the clinic after the predose PK sample is taken. Subjects who forget and take their study drug at home will

be excluded from PK analysis for that day and should not have blood samples collected for PK analysis.

Complete dosing information, including the date and time of actual blood draw and time of the last study drug dose prior to the sampling, should be obtained on all sampling days and recorded on the appropriate blood collection eCRF. If any of the scheduled sampling times are missed or a sample is not drawn according to schedule, the actual collection date and time should be recorded, and the remaining samples should be collected on schedule whenever possible.

Refer to the Laboratory Manual for complete instructions on PK sample collection, processing, handling, storage and shipment.

Plasma concentrations of infigratinib and its active metabolites (including BHS697 and CQM157) will be measured by a central laboratory using a validated liquid chromatography-tandem mass spectrometry assay with a lower limit of quantification (LLOQ) of approximately 1.0 ng/mL. Concentrations below the LLOQ will be reported as below the quantification limit, and missing samples will be labeled accordingly.

PK parameters listed in Table 13 will be estimated for infigratinib. Concentrations of metabolites will be reported and summary statistics (e.g. mean, standard deviation, %CV) calculated, as appropriate.

Table 13: Pharmacokinetic Parameters for Infigratinib

Term	Definition
C_{max}	Maximum observed plasma concentration after drug administration (defined as the 2 hour postdose concentration)
$C_{trough\ (min)}$	Measured concentration at the end of a dosing interval (taken directly before next administration)
R_{acc}	Accumulation ratio calculated as C_{min} steady-state/C_{min} (predose Day 2)

10.3 Assessment of Biomarkers

10.3.1 Sample Collection Procedures and Requirements

Biomarker assessments will be performed to confirm subject eligibility and to aid in understanding the effects of study medications (eg, infigratinib and gemcitabine/cisplatin) on biomarkers of cholangiocarcinoma disease and FGFR pathway regulation as related to clinical outcome.

Options for determination of FGFR2 fusion/rearrangement results for eligibility (archival tumor tissue sample or new biopsy obtained before randomization) include:

- Central laboratory.
    - A known or likely activating FGFR2 fusion/rearrangement is defined as occurring when the breakpoint is within the FGFR2 intron 17/exon 18 hotspot and the gene partner is: 1) known in the literature, in strand with FGFR2; or 2) is a novel partner that is predicted to be in strand and in frame with FGFR2; or 3) is within the FGFR2 intron 17/exon 18 hotspot but the partner gene is out of frame or out of strand with exon 17 of FGFR2; or 4) where the downstream end of the breakpoint may be in an intergenic region and not within another gene (designated as partner n/a) (FoundationOne Liquid CDx 2020).
    - If FGFR2 fusion/rearrangement status was determined by the central laboratory as part of routine clinical care, a tumor sample does not need to be submitted for central confirmation.
- CLIA-certified (or equivalent) local laboratory using a clinically validated test as determined and approved by the sponsor Translational Medicine Department (approved local testing).

All subjects must have documented FGFR2 fusion/rearrangement before randomization and all subjects must have adequate tumor tissue from a prerandomization biopsy sample to send to the central laboratory for confirmation of FGFR2 fusion/rearrangement either before or after enrollment.

If eligibility is determined by a local laboratory, then a prerandomization tumor tissue sample must be sent to the central laboratory within approximately 14 days of start of study treatment for the confirmation of FGFR2 fusion/rearrangement. Refer to the Laboratory Manual for additional details on the amount of tumor tissue required for FGFR2 fusion/rearrangement testing by the central laboratory.

Note: If a prestudy written documentation of FGFR2 fusion/rearrangement in tumor tissue is available from the central laboratory, an additional tumor sample does not need to be submitted.

For China, all FGFR2 testing will be done by the contracted China central laboratory. For study centers in China, written documentation of FGFR2 fusion/rearrangement by the contracted central laboratory is required for study eligibility.

Optional tumor samples may be collected upon disease progression to support exploratory objectives to evaluate potential biomarkers related to cholangiocarcinoma biology and their potential correlation to efficacy, disease progression, and resistance to study medications. Subject consent is required for this optional tumor biopsy.

Archival or newly obtained tumor samples collected during the study will be used to evaluate potential biomarkers related to cholangiocarcinoma biology and their potential correlation to efficacy, disease progression, and resistance to study medications (infigratinib and gemcitabine/cisplatin). This research will be performed using a

combination of genomic, transcriptomic and proteomic technology, which may include profiling of mutation, amplification and/or modification in DNA, RNA, or protein levels in tumor tissue.

Blood samples for assessment of cell-free DNA will be collected as outlined in Table 2, Table 4, Table 5. Blood will be collected at Day 1 of Cycle 1 (predose), and every 8 weeks (±1week) at the same visit as CT/MRI scans, regardless of treatment interruption; at the EOT, if not done within the previous 28 days; and at the time that PD is confirmed (by BICR and/or investigator). These samples will be used for analysis of DNA to explore whether genetic alterations found in tumor samples may also be observed in blood, and if any alterations found are associated with efficacy, disease progression, and development of resistance to study medications.

Sponsor-designated lab(s) will be used for processing of all tumor and blood samples collected. The sponsor will provide kits to collect and ship these samples to sponsor-designated lab(s) for analysis. Refer to the Lab Manual for additional instructions on the collection, handling, storage, and shipment of samples. Sample collection must be captured on the appropriate eCRF and requisition page(s). The samples may be stored under the control of the sponsor or its authorized agents. Samples collected will be stored until the end of the study, or 3 years after the PFS primary analysis, whichever is longer. Samples may be stored longer if the sponsor is required to answer questions from a regulatory or governmental agency. The data may be shared with Health Authorities worldwide, at medical meetings, or in medical publications.

10.3.2 Potential Use for Future Research

Subjects will have an opportunity to consent to use of their remaining tissue or blood samples for additional research related to FGFR genetic alterations and other cancers. A decision to perform such future research studies would be based on new scientific findings related to FGFR genetic alterations and disease, as well as reagent and assay availability.

Future research will use genetic testing (DNA, RNA, protein) of tissue and plasma samples (for cell-free DNA) that are left over from the exploratory objectives analysis. The investigators and subjects will not receive the results from future research. The biological samples will be coded with unique numbers that do not link the samples to the study subject in the study database as part of de-identification of the samples.

The leftover samples for future research may be stored under the control of the sponsor or its authorized agents. The samples will be stored up to 15 years. The period of time that data derived from future research may be used is not specified and these data may be used indefinitely. The data may be shared with Health Authorities worldwide, at medical meetings, or in medical publications.

Participation in future research using leftover tissue and blood is optional. Subjects can request that the sponsor not use their stored samples for future research, to the extent that

they are able to locate the sample after it has been de-identified. Subjects who fail prescreening and fail screening will not have their samples stored for future research.

10.4 Quality of Life

Subject QOL will be evaluated using the EQ-5D, which measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, anxiety, and general health; the EORTC QLQ-C30, a reliable and valid measure of QOL in cancer subjects; and the EORTC QLQ-BIL21, a disease-specific module for subjects with cholangiocarcinoma and gallbladder cancer. QOL instruments (ie, EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BIL21 questionnaires) appear in Appendix 4 (Section 17.4). QOL will be evaluated at the times outlined in Table 2 and Table 4. QOL will not be evaluated for subjects in the gemcitabine plus cisplatin group if and after they cross over to infigratinib.

At each time point, the EQ-5D is to be completed first, followed sequentially by the EORTC QLQ-C30 and EORTC QLQ-BIL21.

If a subject cannot complete a QOL instrument because of illiteracy or other documented reason, the instrument should be omitted. Reasons for missing data will be documented and incorporated into the analysis as necessary.

EQ-5D

The EQ-5D is a standardized instrument for use as a measure of general health states preferences and provides a simple descriptive profile and index value for health status and measures 5 dimensions of health including mobility, self-care, usual activities, pain/discomfort, anxiety, and general health is measured via a vertical visual analog scale (Rabin et al 2001). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

The subject-reported assessments are for the purpose of exploring the subject's own perceptions about their symptoms and health-related QOL and thus a proxy (ie, a caregiver or study personnel) should not complete the questionnaires. Additionally, the investigator must not influence the subject's assessments. Every effort should be made to maintain an unbiased assessment.

At each scheduled assessment, the EQ-5D should be administered prior to all other study procedures. If assessments were completed within the previous 7 days at a regularly scheduled visit, assessments do not need to be administered at the EOT visit.

Details of the algorithms that generate summary derived scores on each of the above health related QOL scales and the statistical approach for each will be provided in the Statistical Analysis Plan (SAP).

EORTC QLQ-C30

The EORTC QLQ-C30 was developed to assess the QOL of subjects with cancer (Aaronson et al 1993). It has been translated and validated into 8 languages. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea and vomiting, pain) and additional single symptom items. It is scored on a 4 point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much). The EORTC QLQ - C30 instrument also contains 2 global scales that use 7 point scale scoring with anchors (1=very poor and 7=excellent).

EORTC QLQ-BIL21

The EORTC QLQ-BIL21 is a disease-specific module to be used with the EORTC QLQ-C30 tool. It was been validated in subjects with cholangiocarcinoma and cancer of the gallbladder (Kaupp-Roberts et al 2016). The QLQ-BIL21 consists of 21 questions: 3 single-item assessments relating to treatment side effects, difficulties with drainage bags/tubes and concerns regarding weight loss, in addition to 18 items grouped into 5 scales: eating symptoms, jaundice symptoms, tiredness symptoms, pain symptoms, and anxiety symptoms. The items are scored on a 4-point Likert scale, as described above.

10.5 Safety Assessments

The safety evaluation will be based on AE reporting, laboratory parameters, vital signs, physical examinations, 12-lead ECGs, and ophthalmic assessments. Tolerability will be assessed by the incidence of AEs leading to study drug interruption, dose reduction, or discontinuation.

10.5.1 Adverse Events

10.5.1.1 Definitions

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s).

An SAE is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

- Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- Social reasons and respite care in the absence of any deterioration in the subject's general condition

In addition, any suspected transmission of an infectious agent via a medicinal product will be considered an SAE at study centers in the EU.

10.5.1.2 Clarifications for AE Definitions

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (eg, hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug(s).

Progression of underlying malignancy is not considered as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria v1.1, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE.

Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some subjects. In this situation, progression is evident in the subject's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

Overdose of infigratinib is to be reported as an AE when drug is administered or taken at a dose ≥200 mg and the overdose is associated with signs or symptoms potentially related to study drug (see also Section 10.5.1.5).

If there is any uncertainty about an AE being due to progression of the disease under study, it should be reported as an AE or SAE.

10.5.1.3 Recording Adverse Events

After a subject signs the molecular prescreening ICF and/or the main study ICF and until a subject is randomized, AEs will only be captured if they meet the definition of serious and are reported to be causally related with study procedures (eg, an invasive procedure such as biopsy). Any other appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) should be recorded as medical history.

Before randomization, any SAEs reported as causally related with study procedures will be captured on a paper SAE Report form. After randomization, all AEs and all SAEs will be captured and reported in the eCRF.

Conditions already present at the time of informed consent should be recorded in the Medical History eCRF.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The following information is to be captured in the eCRF for each AE: severity grade (CTCAE v5.0, Grade 1-5); duration (start and end date); relationship to study drug (infigratinib, gemcitabine, and/or cisplatin); action taken with respect to study drug; whether medication or therapy was given; outcome; and whether the event was serious and seriousness criteria.

AE monitoring should be done from the time of informed consent and continue through 30 days after the last dose of study drug.

10.5.1.4 Reporting Serious Adverse Events

Before randomization, any SAEs causally related with study procedures will be captured on a paper SAE Report Form and must be reported to Covance Safety via email (SAEintake@covance.com) or FAX (refer to the Study Manual for country-specific FAX numbers) within 24 hours of learning of its occurrence.

Every SAE, regardless of suspected causality, occurring after the subject has been randomized through 30 days after the subject has taken his/her last dose of study drug must be reported in the SAE eCRF immediately, and under no circumstances later than 24 hours of learning of its occurrence. If there are any issues with EDC, please send a completed paper SAE report form to Covance Safety via email (SAEintake@covance.com) or FAX. Refer to the Study Manual for country-specific FAX numbers. Any SAEs experienced after this 30-day period should be reported to Covance Safety if the investigator suspects a causal relationship to the study drug.

Any additional information for the SAE including recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode

within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is submitted in the same way as the original SAE Report. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug, a Covance Safety Associate may urgently require further information from the investigator for Health Authority reporting. Covance Safety may need to issue an investigator notification, to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or according to national regulatory requirements in participating countries.

More detailed information on SAE Reporting can be found in the Study Reference Manual.

10.5.1.5 Adverse Events of Special Interest

The following AEs, if otherwise not qualified as an SAE, are to be reported within 24 hours in the electronic data capture (EDC) system.

- Potential drug induced liver injury that meets the following criteria (elevation of bilirubin and ALT/AST that meet Hy's Law criteria [FDA Guidance for Industry, 2009]):
  - Treatment-emergent ALT or AST >3 × baseline value in combination with total bilirubin ≥2 × upper limit of normal (of which ≥35% is direct bilirubin)
  - Treatment-emergent ALT or AST >3 × baseline value in combination with clinical jaundice.
- Retinal detachment of Grade 3 or higher, regardless of relationship to study drug
- Keratitis Grade 3 or higher with suspected relationship to study drug
- Pathological fractures, defined as fractures potentially related or related to metastatic tumor to bone and/or study drug
- Vascular calcifications accompanied by ischemic AEs
- Overdose, defined as a dose ≥200 mg of infigratinib, and that is associated with an AE which is potentially related to study drug.

10.5.1.6 Follow up of Adverse Events

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the appropriate page of the eCRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

All SAEs should be followed according to standard of care until resolution or stability.

Also see Section 7.2.5.2 (infigratinib group) and Section 7.3 (gemcitabine plus cisplatin group) for follow up information on toxicities.

10.5.2 Pregnancies

All WOCBP are to undergo pregnancy testing (blood or urine) at the times specified in Table 2, Table 4, and Table 5. Female subjects must be discontinued from study drug in the event of pregnancy. In addition, for subjects assigned to gemcitabine/cisplatin, pregnancy testing every 4 weeks for 6 months or other schedule should be done after the last infusion of gemcitabine and cisplatin if required according to the local gemcitabine or cisplatin label and local institutional practice.

To ensure subject safety, each pregnancy of a subject or partner of a male subject occurring while the subject is on study drug (and for 30 days after the last study drug dose) must be reported to Covance Safety within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Consent to report information regarding pregnancy and pregnancy outcomes should be obtained from the partner of the male subject.

Pregnancy of a subject or partner of a male subject should be entered on the Pregnancy Notification eCRF. Pregnancy follow-up should be documented on a paper Pregnancy Follow-up Form and reported to Covance Safety via email (SAEintake@covance.com) or FAX Refer to the Study Manual for country-specific FAX numbers.

Any SAE experienced by a subject during pregnancy must be reported as an SAE, as outlined in Section 10.5.1.4.

10.5.3 Laboratory Parameters

Clinical laboratory analyses are to be performed at the times specified in Table 2, Table 4, and Table 5. Parameters included in the panel are listed in Table 14.

Laboratory tests will be collected and analyzed on the scheduled day, even if study drug is being withheld. More frequent assessments may be performed at the discretion of the investigator and if medically indicated, and should be recorded on the unscheduled visit eCRFs.

At any time during the study, abnormal laboratory parameters which are clinically relevant (eg, require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the CTCAE v5.0.

Table 14: Safety Laboratory Parameters

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, RBC counts, WBC counts with differentials, platelets
Biochemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), calcium (can be corrected), chloride, creatinine, blood urea nitrogen or urea, potassium, sodium, magnesium, phosphate Direct bilirubin, indirect bilirubin, total bilirubin, total protein, uric acid, amylase, lipase
Urinalysis	Macroscopic panel (dipstick) (blood, glucose, ketones, pH, protein, specific gravity). Microscopic panel (RBC, WBC)
Coagulation	Prothrombin time or international normalized ratio, partial thromboplastin time

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; RBC, red blood cell; SGOT, serum glutamic-pyruvic transaminase; SGPT, serum glutamic-oxaloacetic transaminase; WBC, white blood cell

10.5.4 Vital Signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed in the same position, either sitting or supine, before dosing at the times specified in Table 2, Table 4, and Table 5. Vital signs should be assessed on the scheduled day, even if study drug is being withheld. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.

10.5.5 Physical Examinations

A complete physical examination (including height and weight) must be performed at the Screening and EOT visits. At all other times indicated in Table 2, Table 4, and Table 5, targeted, symptom-based physical examinations are to be performed, as needed.

The complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back,

lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information about the physical examination must be present in source documentation at the study center. Clinically significant findings that are present prior to randomization should be included in the Medical History eCRF. Significant new findings must be recorded on the AE eCRF.

10.5.6 Electrocardiograms

For each subject, 12-lead ECGs are to be performed at the times indicated in Table 2, Table 4, and Table 5.

Clinically significant ECG findings must be discussed with the sponsor medical monitor prior to enrolling the subject. Clinically significant ECG abnormalities present prior to randomization should be reported on the Medical History eCRF page. Significant new findings post randomization from initiation of study drug until 30 days after permanent discontinuation of study drug must be recorded as an AE on the AE eCRF.

10.5.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status are to be assessed at the times indicated in Table 2, Table 4, and Table 5, according to the following scoring:

Grade	ECOG Performance Status
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 selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Source: https://ecog-acrin.org/resources/ecog-performance-status

10.5.8 Ophthalmic Assessments

For each subject, ophthalmic examinations are to be performed by an ophthalmologist at the times indicated in Table 2, Table 4, and Table 5 and with any new onset of visual disturbance. For postbaseline assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted).

These assessments will include visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, intraocular pressure, retinal OCT, and dilated fundoscopy. Additional examinations such as specular microscopy and corneal pachymetry will be performed as clinically indicated.

Retinal OCT scan images will be collected centrally for potential review. Refer to the Study Manual for details regarding image collection and transfer or shipment.

10.5.9 Early Stopping Guidelines and Data Monitoring Committee

One formal interim analysis of PFS based on BICR will be performed when approximately 114 PFS events have occurred across both treatment arms in the ITT population.

The study may be stopped due to futility at the interim PFS analysis when the futility boundary for testing PFS is crossed. The futility stopping boundary is non-binding to allow for additional considerations. Though efficacy boundaries are specified for PFS assessed by BICR and OS at the time of the interim PFS analysis, the trial will not stop for efficacy at the interim analysis for PFS even if the efficacy boundary is crossed for PFS.

An independent Data Monitoring Committee (DMC) will periodically monitor the interim data at regularly scheduled meetings, according to a prespecified DMC charter and at the interim PFS analysis (see Section 11.2). The voting members of the committee will be external to the sponsor and must not be involved with the trial in any other capacity (ie, they cannot be trial investigators) and must have no competing interests that could affect their role with respect to the trial.

The DMC will review interim trial results, consider the overall risk and benefit to trial participants and make recommendations to the sponsor whether the trial should continue in accordance with the protocol and regarding steps to ensure both subject safety and ethical integrity of the trial.

In the event that the study is terminated early based on a DMC recommendation, the sponsor will notify the appropriate regulatory authorities.

The DMC or sponsor study team may request an ad hoc meeting for any reason, including significant unexpected safety event or follow-up of an observation during a planned DMC meeting.

At each review, subject incidence rates of AEs (including all serious, treatment-related, serious treatment-related and events requiring the discontinuation of study drug) will be tabulated by system organ class, preferred term and severity grade. Listings and/or narratives of “on-study” deaths, deaths within 30 days of receiving study drug and serious and significant AEs, including any early discontinuations due to AEs will be provided.

Records of all meetings will be archived. The DMC will communicate major safety concerns and recommendations regarding study modification or termination to the sponsor.

Further details will be provided in the DMC charter.

11 STATISTICAL METHODOLOGY

11.1 General Considerations

Data will be analyzed by the sponsor and/or designated contract research organization (CRO).

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The primary efficacy analyses will be conducted on the intent-to-treat (ITT) population, defined as all subjects who were randomized; subjects will be analyzed according to their randomized treatment group assignment.

A sensitivity analysis for efficacy will be conducted for subjects who have centrally confirmed FGFR fusion/rearrangement in the ITT population. The safety analysis population will include all subjects who receive at least one dose of study drug and will be analyzed according to the treatment they receive. Detailed definitions of the analysis populations will be provided in the SAP.

The primary endpoint is PFS based on BICR. The primary analysis for PFS will be performed when 228 PFS events have been reached. A formal interim analysis of PFS based on BICR will be also performed when approximately 114 PFS events have occurred in the ITT population.

PFS assessed by BICR will be tested at a 2-sided significance level of 0.05. The key secondary endpoint, OS, will only be tested if the test on PFS assessed by BICR is significant. One interim analysis and one primary analysis for OS are planned. The interim analysis for OS will be conducted at the time of the PFS primary analysis. The primary analysis for OS will be conducted after approximately 224 deaths have been observed.

Any deviations from the protocol or SAP-specified analyses will be described in the clinical study report.

11.2 Sample Size Determination

Approximately 300 subjects with FGFR2 fusion/rearrangement determined by a central laboratory or local laboratory will be randomized in this study (2:1 randomization, with 200 in the infigratinib group and 100 in gemcitabine with cisplatin group) and stratified

by unresectable locally advanced vs metastatic disease, geographic region (North America, Western Europe, Asia Pacific, and rest of the world), prior neoadjuvant/adjuvant treatment (yes/no), and received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no).

The primary endpoint is PFS assessed by BICR.

Assuming a PFS hazard ratio (HR) of 0.67 (median PFS 11.9 vs 8 months) (Valle et al 2010) comparing infigratinib to gemcitabine with cisplatin, with 228 PFS events required, the study will provide approximately 80% power to determine if treatment with infigratinib improves PFS assessed by BICR compared to treatment with gemcitabine and cisplatin at a 2-sided significance level of 0.05. Assuming the test on PFS is significant, with 224 deaths observed, the study will provide 66% power to demonstrate infigratinib improves OS compared to treatment with gemcitabine and cisplatin assuming an OS HR of 0.7 (median OS 16.7 vs 11.7 months) (Valle et al 2010).

The study employs a group sequential design with one interim analysis for futility on PFS, which will be conducted when approximately 50% of the PFS events (114) are observed. The primary analysis for PFS will be conducted after approximately 228 PFS events have been observed. A fixed 2-sided significance level of 0.0001 will be spent at the interim analysis for PFS. A Lan-DeMets alpha spending function approximating O'Brien Fleming boundaries will be used for the non-binding futility boundary.

One interim analysis and one primary analysis for OS are planned. The interim analysis for OS will be conducted at the time of the PFS primary analysis, and the primary analysis for OS will be conducted after approximately 224 deaths have been observed. OS will be tested only if PFS is found to be significant. The Lan-DeMets spending function approximating the O'Brien-Fleming spending function will be used to calculate the significance boundaries.

With 42-month uniform enrollment, the study is projected to reach the planned number of PFS events assessed by BICR (228) in approximately 54 months from randomization of the first subject. The OS event goal of 224 deaths is projected to be reached approximately 66 months from randomization of the first subject. The required sample size is estimated to be a total of 300 subjects, considering that approximately 10% of subjects will drop out per year before a PFS or OS event.

11.3 Statistical Hypothesis, Model, and Method of Analysis

11.3.1 Disposition of Subjects

The number and percentage of subjects entering and completing study drug and the study will be presented by arm. Reason for discontinuation of study drug and study withdrawal will also be summarized.

11.3.2 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, baseline characteristics, prior anticancer therapy, and concomitant medications will be summarized by treatment arm.

11.3.3 Efficacy Analyses

The primary objective of the study is to determine if treatment with infigratinib improves PFS as assessed by BICR compared to treatment with gemcitabine and cisplatin in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion/rearrangement.

The primary endpoint, PFS assessed by BICR, will be tested first at 2-sided significance level of 0.05. The key secondary endpoint, OS, will only be tested if the test on PFS assessed by BICR is significant.

PFS assessed by BICR is defined as the time from randomization to PD confirmed by BICR or death due to any cause, whichever is earlier (including PD/death that occurs after other anticancer treatment) (FDA Guidance for Industry 2015; FDA Guidance for Industry 2018). If there is no documented PD confirmed by BICR or death, PFS assessed by BICR will be censored at the last valid tumor assessment. If the first PD confirmed by BICR or death occurs after 2 or more missing assessments, PFS assessed by BICR will be censored at the last valid tumor assessment. Sensitivity analysis of PFS assessed by BICR will be conducted, in which PFS assessed by BICR will be censored at the last valid tumor assessment before the start of subsequent anticancer therapy if PD confirmed by BICR or death occurs after subsequent anticancer therapy.

The primary analysis of PFS based on BICR will be performed when approximately 228 PFS events have been reached in the ITT population. A data-cut will also be set for the interim analysis for PFS when approximately 114 PFS events assessed by BICR have been reached for the interim analysis on PFS. A fixed 2-sided significance level of 0.0001 will be spent at the interim analysis for PFS. A Lan-DeMets alpha spending function approximating O'Brien Fleming boundaries will be used for the interim non-binding futility and final significance boundaries.

OS time is time from randomization to death. Subjects who have not died (no record of death) or who are lost to follow up will be censored at the date they were last known to be alive. Subjects who withdraw consent for study participation, including consent to be followed up, will be censored on the date of withdrawal. OS will be tested at the primary PFS analysis (only if PFS is found to be significant) and at the OS primary analysis when 224 deaths have been observed. The Lan-DeMets spending function approximating the O'Brien Fleming spending function will be used to calculate the significance boundaries.

The primary endpoint, PFS as determined by BICR, and the key secondary endpoint OS will be tested using a log rank test stratified by randomization stratification factors. The HR and the corresponding 2-sided 95% confidence interval (CI) will be derived from a

Cox proportional hazards regression model stratified by randomization stratification factors for PFS assessed by BICR and OS. The Kaplan-Meier (K-M) medians (if estimable) will be derived, along with their 2-sided 95% CIs.

Subjects randomized to gemcitabine with cisplatin may cross over to infigratinib, or other FGFR inhibitors. To incorporate the effect of such crossover on OS, sensitivity analyses, including inverse probability of censoring weighting (IPCW) (Robins 2000) and rank-preserving structural failure time (RPSFT) model (Robins 1991), may be conducted. The details of such sensitivity analyses will be provided in the SAP.

PFS based on investigator reads and PFS2 (defined as time date of randomization until date of progression on the subsequent therapy or death due to any cause, whichever is earlier, as determined by the investigator) will be analyzed using the same approaches for PFS.

ORR (PR and CR according to RECIST 1.1) will be summarized by treatment group. The 2-sided 95% CI will be calculated for the difference in ORR between the 2 treatment groups based on the Wilson method for subjects in the ITT population. Descriptive statistics will be provided for best overall response prior to any other anticancer treatment for each treatment group. The number and proportion of subjects within each category of response (CR, PR, SD, and PD) and subjects with disease control (CR+PR+SD) will be presented. For duration of response (time from initiation of response to PD confirmed by BICR or death), K-M medians with 2-sided 95% CIs will be presented for responders in each treatment group.

11.3.4 Pharmacokinetic Analyses

PK parameters will be summarized. For subjects with sparse PK samples, only $C_{trough,}$ and C_{max} will be estimated (see Section 10.2). PK parameters will be summarized and listed using relevant statistics by study day, and descriptive statistics will be presented. Concentrations will be summarized as appropriate.

Only PK blood samples with the date and time of collection and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Samples taken from subjects who vomited within 4 hours of dosing will be excluded from the analysis.

PK data generated from this study may be used in conjunction with PK data from other clinical studies (eg, healthy volunteers, advanced cholangiocarcinoma, solid tumors, etc) for population PK and PK/pharmacodynamic assessment. If a population PK model exists when data from this study becomes available, this data may be used to update an existing model and estimate Bayesian PK parameter estimates and exposures (C_{trough}, C_{max}, and AUC) of each analyte for each patient. The estimated PK exposures will also be used to develop or further expand exposure-response models for efficacy and measures of safety. Any population PK data generated will be reported separate from the clinical study report. These analyses will be defined in a stand-alone analysis plan document(s), as appropriate, prior to clinical database lock. Residual PK plasma samples from this study

may also be used for exploratory analysis to further characterize the PK of BGJ398 and/or its metabolites. This may include using residual PK samples for protein binding analysis or metabolite profiling (eg, other metabolites and markers for metabolic enzyme activity such as 4-beta hydroxyl cholesterol levels), if sufficient samples remain.

11.3.5 Biomarker Analyses

Correlative analysis of genomic biomarkers from molecular prescreening and available clinicopathologic and demographic data will be assessed to better understand the genomic landscape of cholangiocarcinoma. Genetic testing (DNA, RNA, protein) of tissue and plasma samples (for cell-free DNA) will be performed using available matched samples in order to detect changes from baseline in molecular profiles in tumor tissues and cell-free DNA from infigratinib-treated and gemcitabine-cisplatin-treated subjects, including those who have progressed. The difference in biomarker results from samples taken before and during treatment will be investigated. Tumor samples collected at disease progression will also undergo genetic and protein analysis to support exploratory objectives to evaluate potential biomarkers that correlate with efficacy and resistance to study medications.

Correlation between biomarkers related to cholangiocarcinoma biology (eg, co-mutations in other genes) and clinical endpoints may also be assessed. Correlative analysis for tumor biomarkers identified at the time of diagnosis and disease progression will be performed. Analysis of genetic alterations and dysregulation of other tumor signaling pathways will be performed to better understand efficacy and resistance to study medications.

As described in Section 10.3.1, concordance between the China central laboratory and the global central laboratory will be assessed using leftover tumor samples and commercially procured cholangiocarcinoma tumors.

11.3.6 Companion Diagnostic Assay Analyses

Concordance rate between central assessment and local assessment on FGFR2 fusion/rearrangement status will be summarized for all subjects who have local testing results and have central testing results available.

As described in Section 10.3.1, samples submitted to the central laboratory may be used to validate a companion diagnostic for FGFR2 fusion/rearrangement testing as part of this study. Leftover tumor samples from enrolled subjects may be used in a bridging study to validate the companion diagnostic.

11.3.7 Analyses of Quality of Life Assessments

QOL assessments (EORTC QLQ-C30, EORTC QLQ-BIL21, and EQ-5D) will be analyzed using a random effects mixed model controlling for baseline scores and randomization stratification factors to assess the difference in treatment arms. Two-sided 95% CIs will be calculated for the difference between the two treatment arms.

In addition, descriptive summaries on the observed data (including change from baseline) will be summarized at each assessed time point. Compliance of quality of life assessments will be reported. QOL instruments are described in Appendix 4 (Section 17.4).

11.3.8 Safety Analyses

Safety analyses will be performed for all subjects who receive at least one dose of study drug according to the treatment they receive. For subjects randomized to gemcitabine with cisplatin who cross over to infigratinib, the safety data before and after crossover will be analyzed separately.

11.3.8.1 Treatment Exposure and Compliance

Duration of treatment will be summarized by treatment arm. In addition, the actual cumulative dose and the relative dose intensity (actual cumulative dose/planned cumulative dose) will be summarized. The number of subjects with dose holds or dose reductions will be tabulated for each study drug by treatment group.

11.3.8.2 Adverse Events

Study data will be monitored on an ongoing basis by the clinical study team to ensure subjects' safety. Additional safety reviews will be performed by the DMC periodically throughout the study (Section 10.5.9). These reviews will include all available data on incidence of AEs, SAEs including deaths, and events leading to study drug discontinuation.

All reported AEs will be assigned system organ class, and preferred term, according to the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be considered to be treatment emergent if the event occurs on or after the first administration of protocol specified treatment and within last dose date +30 days. The subject incidence rates of AEs will be tabulated by system organ class, preferred term, and severity grade for all treatment emergent, serious, treatment related, and serious treatment related AEs. Each of these outputs will include tabulation by maximum severity for each system organ class and preferred term as reported by the investigator based on CTCAE, version 5.0. Summary tables will be provided separately for AEs leading to study drug discontinuation. All "on study drug" deaths, ie, deaths that occur within 30 days after last dose of study drug, will be summarized. Listings and/or narratives of "on study drug" deaths, serious AEs, and AEs leading to study drug discontinuation, will also be provided.

The summaries of the subject incidence rates of treatment emergent AEs by system organ class and preferred term reported AEs will also be provided for subgroups defined by age, sex, and race (if feasible).

Exploratory analyses of AEs by phosphate binder use may be performed.

11.3.8.3 Other Safety Findings

Laboratory parameters for hematology and serum blood chemistry will be summarized at baseline, by visit, and at the last observed value. Additionally, the maximum and minimum observed post-baseline values will be summarized along with the change from baseline to the maximum observed value, minimum observed value and last observed value. Tables of shifts in severity (by CTCAE version 5.0) from baseline for selected laboratory parameters and selected time points may also be provided. Graphical representations of aggregate data may also be presented for parameters of interest.

Exploratory analyses of selected laboratory parameters by phosphate binder use may be performed.

Vital signs, physical examination results, ECOG performance status, ophthalmic assessment, and ECG results will be summarized by treatment group using descriptive statistics (including changes from baseline).

12 DATA COLLECTION AND MANAGEMENT

12.1 Data Confidentiality

All records identifying the subject will be kept confidential and, in accordance with the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded on the eCRF. If the subject name appears on any other document or trial materials, then that information must be redacted before a copy of the document is supplied to the sponsor. Trial data stored on a computer will be stored in accordance with local data protection laws and regulations. Subjects will be informed in writing that representatives of the sponsor, Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

If the results of the trial are published, the subjects' identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified in accordance with applicable laws and regulations.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Either year of birth or exact date of birth (depending on local privacy regulations) will be recorded to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

12.2 Study Center Monitoring

Before study initiation, at a study center initiation visit or at an investigator's meeting, sponsor personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the study center regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the subject's file. The exception is the QOL instrument (questionnaire) data collected in this study, which will be entered directly into a handheld device. The investigator must also keep the original signed ICF (a signed copy is given to the subject).

The investigator must give the field monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

12.3 Data Collection

The designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. The investigator and site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator's staff.

The principal investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PK and biomarker (blood and tissue) samples and imaging scans obtained during the course of the study will be collected from the study centers and analyzed by a sponsor-designated laboratory. Designated study center staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy

and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated study center staff; and one copy will be retained at the study center.

12.4 Database Management and Quality Control

Sponsor personnel (or designated CRO) will review the data entered into eCRFs by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the study center via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Prior medications, concomitant treatments, and post-treatment anti-cancer medications entered into the database will be coded using the World Health Organization (WHO) Drug/Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

PK and biomarker samples will be processed centrally and the results will be sent electronically to the sponsor (or a designated CRO).

The occurrence of any protocol deviations will be determined. Once the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Appropriate sponsor authorization is required prior to making any database changes to locked data.

After database lock, the investigator will receive a copy of his/her subjects' data for archiving at the study center.

12.5 Study Documentation, Record Keeping and Retention of Documents

Each participating study center will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the International Council for Harmonisation (ICH) E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a sponsored study, each study center will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being

accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the study center under the supervision of the investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For eCRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

The investigator must maintain all documentation relating to the study as outlined in local/regional requirements.

The sponsor will retain records in accordance with ICH E6 GCP, Section C.05.012 of Division 5 of the Food and Drug Regulations (FDR), and other applicable regional regulatory requirements.

12.6 Audits and Inspections

Source data/documents must be available for inspection by the sponsor, its designees, or Health Authorities.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed ICF must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to sponsor monitors, auditors,

sponsor Clinical Quality Assurance representatives, designated agents of the sponsor, IRBs/IECs/REBs and regulatory authorities as required.

The investigator will be responsible for informing IRBs and/or IECs in the event of early termination of the trial.

13.3 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (ie, all of the procedures described in the protocol). Study subjects will be informed in writing and orally before the start of the study about the nature and scope of the planned study procedures, in particular about the possible benefits and risks of participating in the study. Consent will be documented by signature on the ICF. The process of obtaining informed consent should be documented in the subject source documents. The date when a subject's informed consent is actually obtained must be captured in the eCRF and the medical records for the subject.

A copy of the ICF must be given to the subject or to the person signing the form.

The sponsor will provide to investigators, in a separate document, a proposed ICF that is considered appropriate for this study and complies with the ICH GCP E6 guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by the sponsor before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the sponsor monitor after IRB/IEC/REB approval.

Women of childbearing potential and sexually active males should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

13.4 Confidentiality of Study Documents and Subject Records

The investigator must ensure pseudonymization of the subjects by replacing names with the study-specific subject identification number); subjects must not be identified by names in any documents submitted to the sponsor. The names of study subjects and all other confidential information are subject to medical confidentiality and the provisions of the General Data Protection Regulation (GDPR) and other applicable regulations or laws. Subject data may only be passed on in pseudonymized form beyond the study center. Third parties do not have access to original documents.

Signed ICFs and subject enrollment log kept at the study center to enable subject identification must be kept strictly confidential.

14 FINANCIAL CONSIDERATIONS AND INSURANCE

Financial disclosures and insurance for the sponsor will be provided in a separate document.

15 PUBLICATION POLICY

The sponsor is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. The sponsor assures that the key design elements of this protocol will be posted on a publicly accessible database, eg, www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials will be posted publicly according to local regulations.

The sponsor follows the International Committee of Medical Journal Editors authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from the sponsor or through a professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, the sponsor supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

Any data analysis carried out independently by the investigator must be submitted to the sponsor before publication or presentation.

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17 APPENDICES

17.1 Appendix 1: List of Concomitant Medications (Infigratinib Treatment)

In general, the use of any concomitant medication deemed necessary for the care of the subject is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or infigratinib.

The following lists in Table 15 are based on the Indiana University School of Medicine's "Clinically Relevant" Table (Flockhart Table™; Flockhart 2007) and supplemented with the FDA draft guidance and the online database Drugbank.ca. Note: this may not be an exhaustive list of medications, investigator should use this list as a guide.

Table 15: Drugs to be used with Caution While on Study

Category	Drug Names
CYP3A substrates with narrow therapeutic index	alfentanil, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, sirolimus, tacrolimus, terfenadine, warfarin sodium or any other coumadin-derivative anticoagulants, direct thrombin inhibitors (eg, argatroban), and Factor Xa inhibitors (eg, rivaroxaban)
Medications which alter the pH of the GI tract [a,b]	antacids, H2-antagonists (eg, ranitidine)
Medications that have possible risk of TdP/QT prolongation	alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tamoxifen, tizanidine, vardenafil, venlafaxine, ziprasidone
Medications that have conditional risk of TdP/QT prolongation	amitriptyline, amisulpride, ciprofloxacin, clomipramine, desipramine, diphenhydramine, doxepin, fluoxetine, galantamine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, solifenacin, trazodone, trimethoprim-sulfa, trimipramine

Category	Drug Names
Medications with established potential for QT prolongation or TdP	amiodarone, anagrelide, arsenic trioxide, astemizole (off US market), azithromycin, bepridil (off US market), chloroquine, chlorpromazine, cisapride (off US market), citalopram, cocaine, disopyramide, dofetilide, domperidone (off US market), dronedarone, droperidol, erythromycin, escitalopram, flecainide, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off US market), mesoridazine (off US market), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol (off US market), procainamide (oral off US market), quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (off US market), terfenadine (off US market), thioridazine, vandetanib
BCRP substrates	atorvastatin, irinotecan, methotrexate, rosuvastatin, simvastatin, sulfasalazine, topotecan

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome p; FDA, Food and Drug Administration; GI, gastrointestinal; TdP, Torsades de Pointes

[a] Infigratinib should be dosed at least 2 hours before or 10 hours after dosing with a H2 receptor agonist, or separated by 2 hours with acid neutralizing agents (antacids).

[b] Proton pump inhibitors are prohibited due to their long pharmacodynamic effect and should be replaced with H2-antagonists or antacids.

Sources: FDA Guidance for Industry, 2017; Flockhart 2007; drugbank.ca.

17.2 Appendix 2: List of Prohibited Medications and Substances (Infigratinib Treatment)

Table 16: List of Prohibited Medications and Substances[a] While on Study

Category	Drug Names
Moderate inhibitors of CYP3A4 [b]	ACT-178882, ACT-539313, amprenavir, aprepitant, atazanavir, atazanavir/ritonavir, casopitant, cimetidine, ciprofloxacin, crizotinib, darunavir, darunavir/ritonavir, diltiazem, dronedarone, duvelisib, erythromycin, faldaprevir, fedratinib, FK1706, fluconazole, fosaprepitant, GSK2647544, imatinib, isavuconazole, istradefylline, lefamulin, letermovir, netupitant, nilotinib, primidone, ravuconazole, Schisandra sphenanthera, tofisopam, verapamil, voxelotor
Moderate inducers of CYP3A4 [b]	Asunaprevir/beclabuvir/daclatasvir, bosentan, cenobamate, dabrafenib, efavirenz, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, modafinil, nafcillin, PF-06282999, rifabutin, semagacestat, talviraline, telotristat ethyl, thioridazine, tipranavir/ritonavir
Strong inhibitors of CYP3A4 [b]	boceprevir, ceritinib, clarithromycin, cobicistat (GS-9350), conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib, indinavir, indinavir/ritonavir, itraconazole, josamycin, ketoconazole, LCL161, lopinavir/ritonavir, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, troleandomycin, tipranavir/ritonavir, tucatinib, voriconazole grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits
Strong inducers of CYP3A4 [b]	apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifampin, rifapentine, St. John's wort extract
Medications which alter the pH of the GI tract	proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole)
Medications which increase serum phosphate and/or calcium	calcium, parathyroid hormone, phosphate, vitamin D (including multivitamins containing vitamin D)
Chinese herbal and patent medicines for cancer treatment	Chinese herbal medicine and Chinese patent medicines for the treatment of cancer are not allowed during the treatment period.

Abbreviations: CYP, cytochrome p; US, United States

[a] This may not be an exhaustive list of prohibited medications. Use this list as a guide and refer to the prescribing information for any medication to determine unacceptable interactions and/or contact the sponsor.

[b] Sources: University of Washington 2021a; University of Washington 2021b

17.3 Appendix 3: List of Highly Effective Methods of Contraception

The following is from the Clinical Trials Facilitation Group 2014 (Section 4.1).

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - injectable
  - implantable [2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]
- bilateral tubal occlusion [2]
- vasectomised partner [2,3]
- sexual abstinence [4]

1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see Clinical Trials Facilitation Group 2014, section 4.3).

2 Contraception methods that in the context of this guidance are considered to have low user dependency.

3 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

17.4 Appendix 4: QOL Instruments

This appendix describes the QOL instruments used in the study.

EQ-5D-5L Scoring

The EQ-5D-5L consists of 6 items: 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and a health state score. Each of the 5 dimensions has 5 levels. The combination of 1 level from each of the 5 dimensions (eg, 12234) will be used to obtain the health index score.

The EQ-5D-5L cross-walk value set for United Kingdom (UK) will be used in the derivation of health index scores.

Details of analysis will be described in the SAP.

QLQ-C30 Scoring

The EORTC QLQ-C30 has been translated and validated into 8 languages. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. It is scored on a 4-point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7-point scale scoring with anchors (1=very poor and 7=excellent). The scoring for each functioning scales and symptom scales follows the algorithms below.

The EORTC QLQ-C30 Summary Score is calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale are not included). Prior to calculating the mean, the symptom scales need to be reversed to obtain a uniform direction of all scales. QLQ-C30 Summary Score = (Physical Functioning+ Role Functioning+ Social Functioning+ Emotional Functioning+ Cognitive Functioning+ 100-Fatigue+ 100-Pain+ 100-Nausea_Vomiting+ 100-Dyspnoea+ 100-Sleeping Disturbances+ 100-Appetite Loss+ 100-Constipation+ 100-Diarrhoea).

Details of analysis will be described in the SAP.

EORTC QLQ-BIL21

The QLQ-BIL21 module has been found to be a reliable and valid measure to assess the QOL of patients with cholangiocarcinoma and cancer of the gallbladder. It contains 21 items that comprise 5 multi-item symptom scales and 3 items that should be scored as individual items. It is scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4-very much). Specific instructions regarding the scoring of the BIL21 are provided below:

Symptom Scales/Items	Scale	Number of items	Item range*	Item numbers
Eating Symptoms	ES	4	3	31, 32, 33, 34
Jaundice Symptoms	JS	3	3	35, 36, 37
Tiredness	T	3	3	38, 39, 40
Pain Symptoms	PS	4	3	41, 42, 43, 44
Anxiety Symptoms	AS	4	3	45, 46, 47, 48
Treatment Side Effects	TSE	1	3	49
Difficulties with drainage	D	1	3	50
Concerns re: Weight Loss	WL	1	3	51

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

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

$$\text{Raw Score} = RS = (I1 + I2 + \ldots In)/n$$

For all Symptom Items or Scales, the score is calculated as follows:

$$\text{Score} = [(RS - 1)/\text{range}] * 100\%$$

For example, if a subject has response value of 1, 2, 2, 4 for item 31, 32, 33 and 34, respectively, the Raw Score (RS) for Eating Symptoms would be calculated as follows:

$$RS = (1+2+2+4)/4 = 2.25$$

$$\text{ES Score} = (2.25 - 1)/3 = 41.7\%$$

Details of analysis will be described in the SAP.

17.5 Appendix 5: Acceptable Prestudy Gemcitabine-based Chemotherapy

The following gemcitabine-based chemotherapies are acceptable for prestudy treatment (NCCN Guideline Version 1, 2021):

- Gemcitabine + cisplatin
- Gemcitabine + cisplatin + nab-paclitaxel
- Gemcitabine + cisplatin + S-1 (Kanai 2015; Sakai 2018)
- Gemcitabine + S-1
- Gemcitabine + capecitabine
- Gemcitabine + nab-paclitaxel
- Gemcitabine monotherapy